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PRESIDENT'S ADDRESS*

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MR. CHAIRMAN, Members of the American Radium Society and Guests, Ladies and Gentlemen:

This, our Thirty-ninth Annual Meeting breaks with tradition in gathering outside the boundaries of the United States. We in Canada are keenly aware and appreciative of the high honor you thus bestow upon us. The Governor General of Canada—Representative of Her Majesty the Queen—has sent expressions of regret that he finds it impossible to be in residence in his summer home in the Citadel and for his resultant inability to receive you.

The Lieutenant Governor of this Province of Quebec is unfortunately unavoidably absent in the Eastern Townships. He also has conveyed to me similar words of regret. The Canadian Medical Association, assembled here last year, took cognizance of our meeting. Dr. Lemieux, the President, has graciously accepted an invitation to join us at our Annual Banquet. We are grateful to the President and members of the Canadian Association of Radiologists for the reception tendered us. We are indeed happy to have so many of them attending this meeting. Monseigneur Alphonse Parent, Recteur de L'Université Laval, will be our host this afternoon. It is particularly fitting that we are to be guests of the oldest institution of learning in Canada—indeed the second oldest, I believe, in either Canada or the United States. Atomic Energy of Canada Limited, of which we are justly proud, also join in making you welcome.

You will probably be interested to know that the American Radium Society was organized and first met in Philadelphia in 1916. We are pleased to record that two of the charter members are still on our roll—Dr. T. Quigley of Omaha, Nebraska, and Dr. James T. Case, a Past-President of the Society, of Santa Barbara, California. At that first meeting a Canadian, the late Dr. W. H. B. Aikens of Toronto, was elected President. Perhaps I may be forgiven under these circumstances for suggesting, that for me this year marks another anniversary in our Society.

The first paper on our Scientific program honors the memory of a distinguished pioneer Canadian radiotherapist. Shortly after Dr. Gordon Richards died in 1949—a martyr to his profession—The Ontario Cancer Treatment and Research Foundation inaugurated a Gordon Richards Memorial

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Lecture to be delivered annually, before a major medical or scientific Association meeting in Canada. This Memorial is not entirely unknown to the American Radium Society; three of the five previous lectures have been delivered by members of this Society. Dr. Quick addressed the Canadian Medical Association in Winnipeg in 1953, on the subject of "The Influence of Radium on Cancer Therapy." Dr. Collins followed in 1954 with a paper entitled "The Influence of Radioactive Isotopes in Medicine" presented before the Ontario Medical Association in Toronto, and Dr. Ralston Paterson's contribution "Why Do Cancer Patients Delay" was also given in Toronto in 1955 at the combined Annual Meeting of the British, Canadian, and Ontario Medical Associations.

When the Ontario Cancer Foundation kindly offered to make the lecture available to the American Radium Society, your executive officers were graciously pleased to accept. With the approval of the Foundation, the program committee chose to invite Dr. Arthur Ham for the 1957 lecture.

Under the circumstances it might be of interest to outline the history of the Foundation, and tell you briefly of the manner in which the treatment of cancer in general and by radiotherapy in particular has been conducted in the Province of Ontario.

In 1932 the Provincial Legislature established a commission to investigate the use of radium and prepare a plan for the satisfactory dispersal of a considerable amount of public monies allocated for this purpose. After a period of intensive travel and study of conditions prevailing both on this Continent and in Europe, the commission submitted its findings. The Minister of Health, with the advice of an Advisory Cancer Committee, recognized the necessity for centralization of radiotherapy, particularly for purposes of research; on the other hand it was not deemed necessary that this centralization be carried to the extreme, suggested at times, whereby radiotherapy should be confined to centers with not less than one or two million persons. It was realized that in a vast and sparsely populated country such as Canada, large numbers of cancer sufferers in need of radiotherapy could not, and in fact would not, travel distances of 100 to probably 300 miles and remain for treatment so far from friends and home.

In consequence, the Department of Health for Ontario took steps in 1935 to organize a program for radiotherapy around the three medical schools in the Province and also to give recognition to the work being done by and co-ordinate the activities of four other suitably distributed centers of radiotherapy, situated in areas capable of providing all the necessary ancillary care to the cancer patient.

The Clinic Directors met in regular conference. An excellent service was provided in radiological physics and a uniform system of records was worked out under supervision of the Statistical Branch. Complete summary cards on all patients were submitted annually for analysis from each of these seven official Ontario Cancer Centers. Development in all Centers was rapid.

In time the Department of Health chose to become less closely associated, and the Ontario Cancer Treatment and Research Foundation was incorporated in 1943 by a special act of the Legislature, which defined the object of the Foundation as, "The conduct of a program of diagnosis, treatment, and research in cancer—."

The Foundation, presently headed by Mr. Rhys M. Sale, President of the Ford Motor Company of Canada Limited, consists of 9 additional members, 2 of whom belong to the medical profession. One of the latter, Dr. W. G. Cosbie, has succeeded the late Dr. Richards as Medical Director and Chairman of the Advisory Medical Board. One of the first acts of the Foundation, on advice of its Advisory Medical Board and with local approval, was to assume active control of the clinic at Queens University in Kingston as a Pilot Center. At the same time the other clinics became affiliated with the Foundation as auton-

omous centers, and a well regulated program of building and expansion was inaugurated. In time it has become mutually advantageous for five more of the now eight centers to relinquish their local control and the clinics in London, Kingston, Hamilton, the Ottawa Civic Hospital, Windsor, and Port Arthur are now administered directly by the Foundation and financed entirely by it, with the exception of receipts from patients. The clinics in the Toronto General and Ottawa General Hospitals are still responsible to the organizations in which they are located, and receive annual grants from the Foundation. On completion of the new Institute in Toronto within the next few weeks, the center in the Toronto General Hospital will be transferred and also become more closely associated.

The Foundation in turn receives annual matching grants from the Federal and Provincial treasuries, which totaled $1,929,062.00 in the year ended March 31, 1957. These grants cover substantially all of the Foundation's current expenditures and equipment purchases. Special Provincial grants were also received for aid in construction of the new Toronto unit. Construction costs for the other centers were undertaken locally, supplemented by grants from the Foundation provided by various bequests and more importantly by monies received through public subscription, latterly by effort of the Canadian Cancer Society.

In addition to its treatment facilities of which I shall speak more fully, the Foundation maintains diagnostic and follow-up clinics, particularly throughout Northern Ontario.

Family physicians and dentists are encouraged to send biopsy material on all suspicious lesions to the certified pathologist of their choice. The popularity of this service is evidenced by the increase in utilization from 6,290 examinations in 1951 to 20,190 in 1956. Biopsies of skin (41.3 per cent) and cervix uteri (34.7 per cent) provided over three-quarters of the specimens submitted. In 1955, 7,179 microscopic diagnoses of cancer were made. The fact that 88 per cent of all biopsies submitted proved benign is an acceptable indication of a very satisfactory public service; 2,879 individual physicians and dentists made use of this diagnostic biopsy service. It has not been feasible to extend the service to include smears of the Papanicolaou type.

The Foundation assumes responsibility for clinical cancer research, and in 1956 made a total of $71,369.00 available to 41 different projects. It has allotted responsibility for fundamental cancer research to the National Cancer Institute of Canada and pays to this body an amount equal to 7 per cent of the annual Provincial and Federal grants available to Ontario. The entire sum expended for research by the Foundation in 1956 was $183,101.00 excluding research undertaken by the staffs of its treatment centers.

The Foundation "delegates to the Ontario Division of the Canadian Cancer Society its responsibility for the conduct of a program in public education" but is active in the field of professional education. A facet of this enterprise is represented by the Gordon Richards Memorial Lecture which you are about to hear.

Each of the treatment centers is suitably housed and adequately equipped with radium, radon, superficial and medium voltage roentgen-ray machines and the necessary ancillary equipment for thorough clinical investigation and treatment. Beds are at their disposal. Although in some instances an overlapping of staff exists, the clinics are entirely independent of the diagnostic roentgenologic departments of the hospitals in which they are located. Seven of the eight clinics employ cobalt 60 beam therapy, and isotope facilities are being expanded. Adequate professional, technical and clerical staffs are maintained and physicist service provided.

Development of prepaid medical services is well advanced in Ontario, perhaps most noticeably so in Windsor, where 82 per cent of the population are covered by Windsor

Medical Services, a project successfully administered by the local medical society for a period of eighteen years. A similar plan, operated by the Ontario Medical Association is rapidly expanding as are other Trans-Canada services. Of the sixteen and one half million people living in Canada, 5,870,000 are covered by the prepaid plans.

For these and other reasons the Foundation has, quite correctly I believe, adopted the policy that cancer treatment should not be free in Ontario. Wherever possible, without hardship to himself or family, the patient is expected to pay a reasonable fee for all services performed. The director of the clinic and his financial secretary are empowered to scale this fee to any degree deemed advisable. Cost of prolonged treatment and the entire expense for indigent patients is covered by the Foundation. The patient has no financial worry in this respect. The radiotherapist is at liberty to administer any type of treatment in the quantity he desires, without thought of expense, and yet the patient's personal esteem is respected, and the principle of private practice maintained. The Clinic Directors are, with one exception, on a part-time basis with the privilege of conducting to a limited degree their own offices and private practices. In some instances this involves roentgen diagnosis; in others the surgery of cancer. The tendency is to divorce diagnostic roentgenology from radiotherapy. The manifold advantages of this plan are sufficient to overcome the radiotherapist's natural aversion as a physician to accepting a salary for his duties in administering the clinic and practicing radiotherapy. We hope that it will materially aid in attracting clinicians of the highest caliber to this branch of radiology, which still occupies the position of a poor sister to diagnostic roentgenology.

The central statistical office prepares an annual report on I.B.M. machines from the material submitted on each individual's summary card. Clinical conferences are held once or twice a year at which the directors from all the centers, along with the radiotherapists, pathologists, physicists, and consultants appropriate to the site under study, are expected to attend.

Although their activities center about radiotherapy, the clinics are by no means so limited. On the contrary, the active and consulting staff in each provides a complete cancer diagnostic and treatment service, retaining wherever possible the relations of a private patient to his medical and surgical attendants.

The clinics have maintained a steady and persistent growth. In 1956, 5,410 new cancer patients were admitted. Of these, 4,104 were treated by radiotherapy alone or in combination with other methods. I trust I may be forgiven for speaking now for a very few moments on an experience of my own at the Windsor Clinic with which I am most familiar. Geographically we are located in a small peninsula closely surrounded on three sides by water and the United States border. There are approximately 247,000 people in the county. This clinic has been in operation for nearly twenty-two years. In 1956 we admitted 417 new cancer patients; 332 received irradiation. The follow-up system is uniquely successful. The records contain a report on the five year condition on 99.9 per cent of the patients. Using absolute figures, with no exclusions for failure to accept or complete treatment or for deaths from intercurrent disease, the outlook for the cancer patient has definitely improved. Disregarding those with rapidly curable cancer of the skin, but including patients with all other varieties of cancer, recurrent as well as primary, 28 per cent of those seen in the clinic between 1935 and 1939 were alive at the end of five years, whereas 42 per cent of those seen between 1947 and 1951 lived five years. The survival rate for cancer of the cervix has risen from 30 per cent to 53 per cent in the same period, for cancer of the breast from 32 per cent to 55 per cent, for cancer of the rectum from 15 per cent to 41 per cent, and for cancer of the intrinsic larynx from 20 per cent to 54 per cent.

These figures do not reflect results from recent additions to the armamentarium. Cobalt 60 may not affect the survival rates appreciably in some of the sites quoted, but it undoubtedly provides an additional something, palliative as well as curvative, for a group of patients to whom there was formerly practically nothing to offer. This experience duplicates that of many centers, but it does also justify the claim of the smaller properly set-up center, to treat the majority of cancer patients, utilizing a degree of personal attention that is often unattainable in large institutes and with the satisfaction incumbent to the patient by proximity to his home and family physician.

These remarks do not imply that successful radiotherapy can be accomplished elsewhere than in a properly and expensively equipped center, staffed with experienced clinical and technical personnel and so situated that an adequate volume of work is at hand. There is no thought of further decentralization in Ontario.

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IRRADIATION OF CARCINOMA OF THE BLADDER BY A CENTRAL INTRACAVITARY RADIUM OR COBALT 60 SOURCE (THE WALTER REED TECHNIQUE)*

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A PRELIMINARY report, published in 1949, of the Walter Reed technique employing a central intracavitary radiation source for the treatment of bladder cancer was based on 13 cases.[1] Ten of these are still alive and have been free of disease from five to ten years.

This high arrest rate was not subsequently maintained. However, in a series of 50 patients, including the original 13, treated between July 18, 1945 and April 22, 1953, the absolute five year tumor arrest rate was 56 per cent. Two patients who died of heart failure during the course of treatment and 1 who died of gastric hemorrhage two weeks after treatment were included as cancer deaths. All patients have been followed.

The term, "Walter Reed technique" is used for a definite reason. Many therapists subsequently used a central radioactive source in a balloon with variable results, because they failed to follow the detailed technical steps originally recommended. Consequently, we have organized the procedures according to certain principles, which must be followed if maximum results are to be achieved.

THE PRINCIPLES OF THE TECHNIQUE

1. Classification of the lesion.
2. Small central source of radium or cobalt 60.
3. Proper balloon applicator to irradiate the lower two-thirds of the bladder.
4. Cystotomy inspection during insertion of the radiation source.
5. Roentgenographic control of the applicator during treatment.
6. Fractionation of the dose.
7. Serial biopsies.
8. Selection of suitable total dose (6,000 r_γ to 10,000 r_γ) for each lesion.

1. CLASSIFICATION AND INDICATIONS FOR TREATMENT

Cancer of the bladder manifests itself in many ways. There is an optimum treatment for each type. A classification should incorporate the following: Major factors: *Stage*—anatomical extent; *Grade*—histologic degree of malignancy. Minor factors: Primary or recurrent; single or multiple; geometrical thickness of the lesion.

The first two factors, Stage and Grade, are most important. The authors employed Marshall's classification[4] of stages (Fig. 1) and, following his suggestion, incorporated it with the histologic classification into a scatter diagram (Fig. 2).

Stage O is carcinoma *in situ;* Stage A is limited to the mucosa and submucosa; Stage B_1 is superficial invasion of the muscularis; Stage B_2 is extension to the serosa; Stage C is extravesical extension; Stage D_1 is metastasis to regional pelvic lymph nodes or invasion of the parenchyma of adjacent organs (*i.e.*, extension down the posterior urethral musosa would not place the lesion in Stage D, but invasion of the acini of the prostate would place the lesion

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in Stage D_1); Stage D_2 is metastasis to extrapelvic lymph nodes or distant organs.

In the classification chart (Fig. 2), the lesions are distributed along an oblique line. This is typical of a representative series of cases, probably classified with reasonable accuracy. There were no unusual cases in this series, such as Stage A—Grade 4, or Stage D_2—Grade 1. Whenever there was doubt as to the grade or stage of a particular lesion, it was placed in the milder category. The clinical staging of our lesions tends to place them in a less advanced category than in a comparable series classified after surgery. The omission of surgical exploration of lymph nodes compels placing some of our patients with small or impalpable metastatic lymph nodes in the Stage C category instead of Stage D.

Papillary carcinomas are histologic Grades 1 and 2; infiltrating tumors are Grades 3 and 4. Papilloma of the bladder was not included. Figure 3*A* illustrates a papillary carcinoma, Grade 2. There were 3 Grade 1—Stage A papillary carcinomas in this series. They would ordinarily be considered of questionable malignancy, but

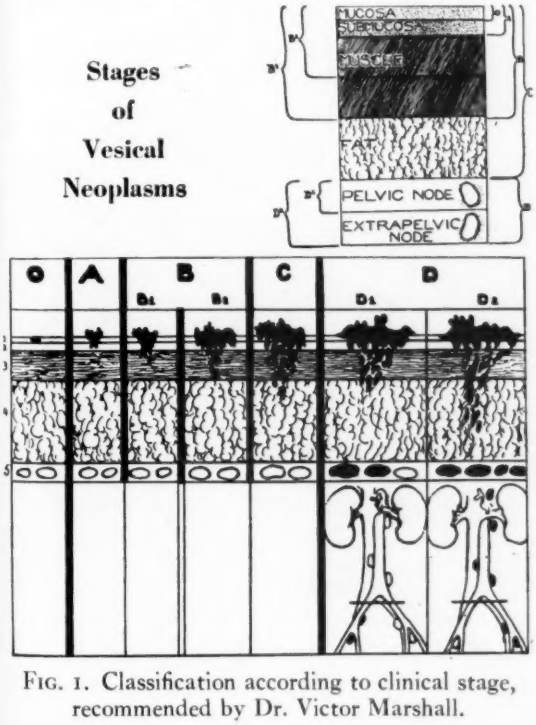

FIG. 1. Classification according to clinical stage, recommended by Dr. Victor Marshall.

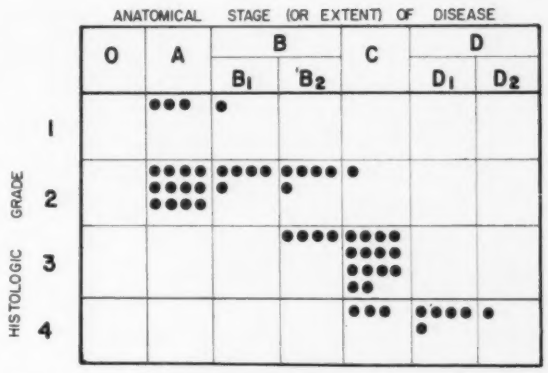

FIG. 2. Scatter diagram of classification of 50 lesions in this series. The linear dispersion of the cases in the scatter diagram is characteristic of a series of typical cases of cancer of the bladder.

in 2 cases there were from 30 to 50 lesions, and in the third case eight enormous papillary fronds aggregated a mass about 8 cm. in diameter. (It was illustrated in our preliminary report as Figure 25).[1] In all 3 cases, the alternative to irradiation was cystectomy. A former Grade 2 papillary carcinoma which has become infiltrating is classified as Grade 3 (Fig. 4*A*).

In this series there were 12 cases of Stage A—Grade 2 lesions which signify early cancer, and 14 cases of Stage C—Grade 3 lesions, which signify advanced cancer. These two groups are useful for evaluating the effectiveness of the Walter Reed technique.

In this series there were 27 recurrent and 23 primary lesions. None of the lesions had previously been irradiated. Previous treatment of the recurrent lesions consisted of one or more transurethral fulgurations or transurethral resection or segmental resection. The importance of primary versus recurrent tumor will be discussed later in the section on results. Recurrent tumors have a poorer prognosis than primary tumors.

The number of tumors in each bladder is an important criterion in the selection of the appropriate treatment technique. A single papillary carcinoma may be effectively treated in one of many ways: simple fulguration, transurethral resection, segmental resection (especially when the tumor is located on the dome), interstitial

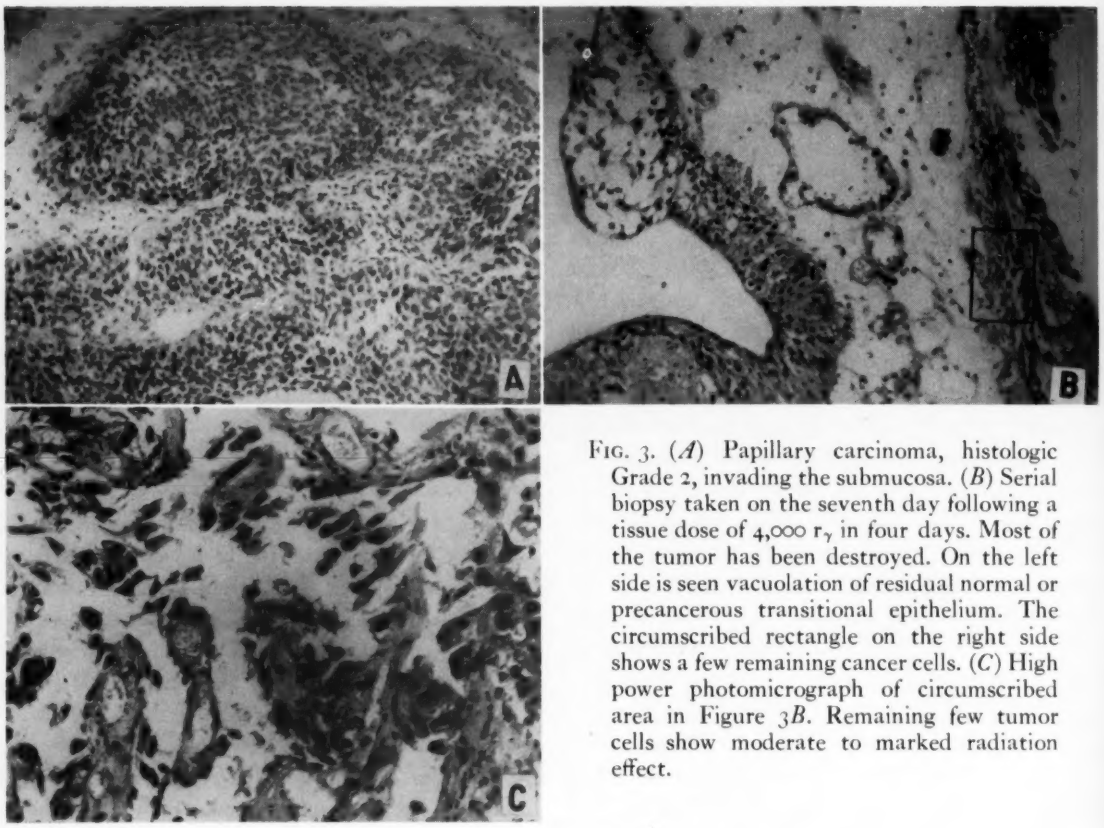

FIG. 3. (*A*) Papillary carcinoma, histologic Grade 2, invading the submucosa. (*B*) Serial biopsy taken on the seventh day following a tissue dose of 4,000 r_γ in four days. Most of the tumor has been destroyed. On the left side is seen vacuolation of residual normal or precancerous transitional epithelium. The circumscribed rectangle on the right side shows a few remaining cancer cells. (*C*) High power photomicrograph of circumscribed area in Figure 3*B*. Remaining few tumor cells show moderate to marked radiation effect.

radium or cobalt 60 needles or seeds, or irradiation with a central intracavitary source. However, since the majority of bladders with single papillary carcinoma later have multiple lesions, it is unwise to use an aggressive procedure, such as cystotomy and intersititial irradiation, which may interfere with proper treatment of the subsequent lesions. For a single papillary carcinoma, fulguration or transurethral resection will not interfere with future therapy. The Walter Reed tech-

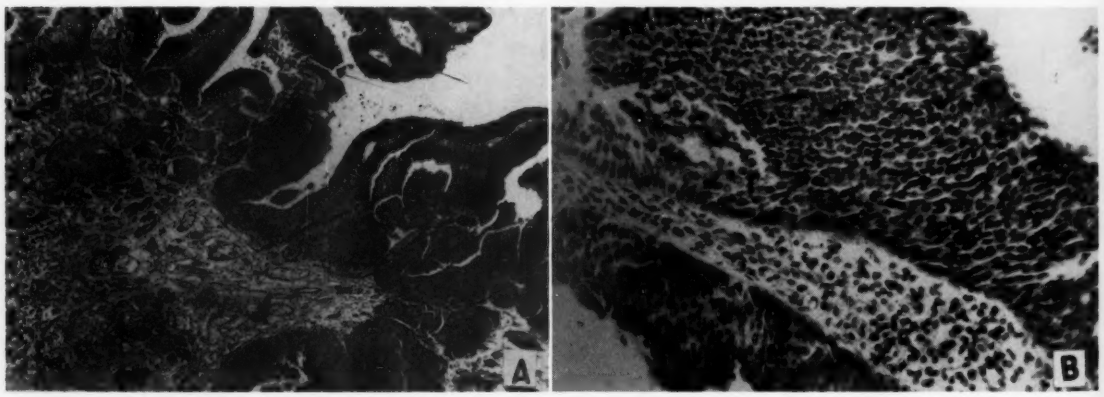

FIG. 4. (*A*) Infiltrating carcinoma, histologic Grade 3. This had originally been a Grade 2 papillary carcinoma, but is now infiltrating the submucosa and muscularis. This variety tends to be radioresistant. (*B*) High power photomicrograph of serial biopsy taken on the ninth day, following a surface dose of 4,360 r_γ in four days. This radioresistant tumor shows very little radiation effect.

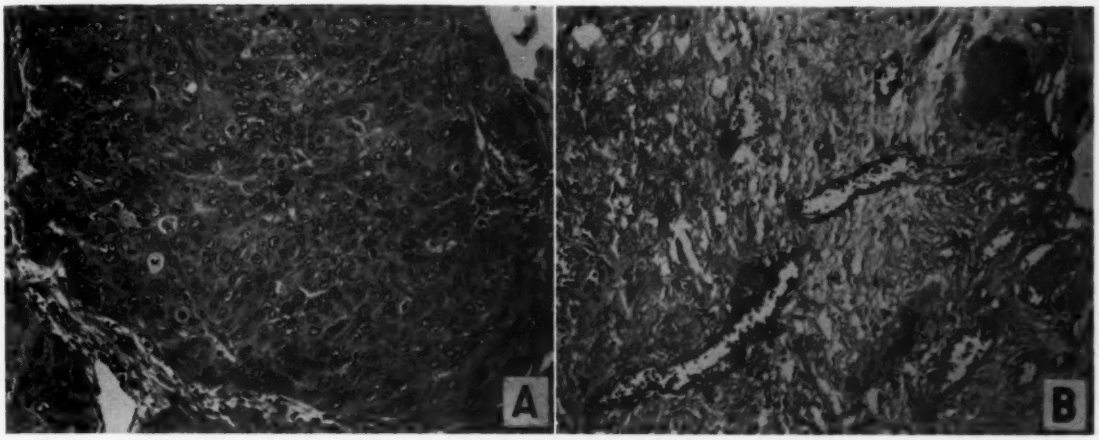

FIG. 5. (*A*) Undifferentiated carcinoma, histologic Grade 4. This type is very radiosensitive. This particular tumor was a large bulky neoplasm measuring 3.0×5.0 cm., and was 2.5 cm. thick. It extended through the posterior bladder wall fixing it in the pelvis. (*B*) Serial biopsy taken on the tenth day, following a surface dose of 4.240 r_γ in four days. There was massive acute cell death with destruction of over 95 per cent of the tumor. One small remaining island of tumor cells can be seen in the upper right hand corner. The bladder was reopened on the tenth day to take this biopsy. At that time the tumor had shrunken markedly, and was less than 1 cm. thick. A total surface dose of 10,507 r_γ in fourteen days destroyed the tumor. The patient is free of disease for seven years.

nique is useful because it irradiates not only the visible tumor, but also the sites of potential new tumors.

When an advanced cancer is thicker than 2.5 cm., a small central source is usually not the most efficient method. It is preferably treated with rotational supervoltage irradiation. However, if a bulky tumor is highly malignant and very radiosensitive, it may be arrested by the former method (Fig. 5*A*).

The *radiosensitivity* of bladder cancer is variable. The best results are obtained in single or multiple papillary carcinomata (Fig. 31*A*). Infiltrating cancers, Grade 3 or 4, in an early stage are most responsive to

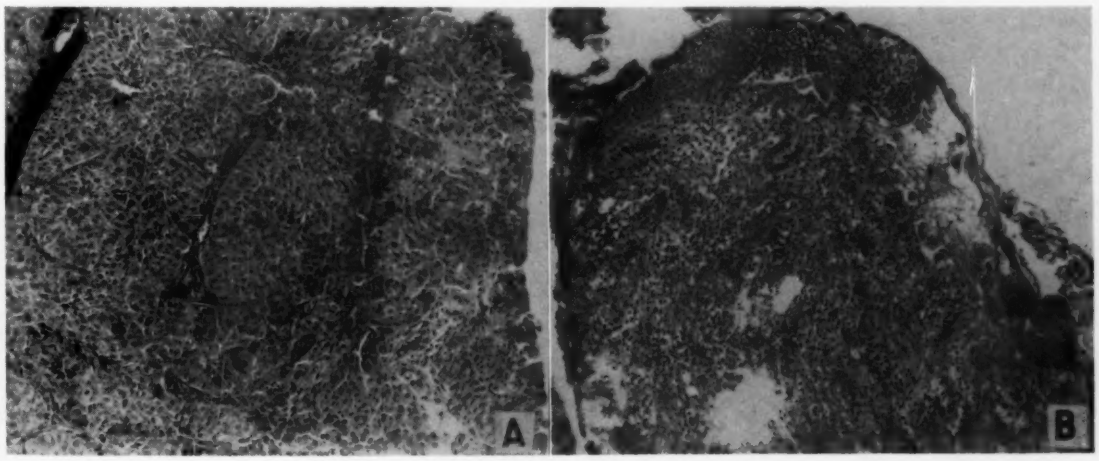

FIG. 6. (*A*) Infiltrating carcinoma, histologic Grade 3. This tumor originated as a diffuse superficially infiltrating carcinoma involving approximately one-third of the bladder mucosa. (*B*) Serial biopsy taken on the eighth day following a surface dose of 4,360 r_γ in four days. The tumor is very radiosensitive, showing marked acute cell death. There are a few remaining isolated carcinoma cells in advanced stages of radiation disintegration.

treatment with a small central source because of their pronounced radiosensitivity; and even some moderately advanced, Stage C lesions are still curable. A Grade 2 papillary carcinoma which later becomes Grade 3 infiltrative (Fig. 4*A*) is less radiosensitive than a primary Grade 3 infiltrating carcinoma (Fig. 6*A*). Diffuse papillary carcinoma thickly covering the entire bladder is not readily responsive to irradiation. Squamous cell cancers are occasionally radiosensitive but usually very radioresistant.

For convenience in designation, 12 *clinicopathologic* types of bladder cancer (Table 1) are distinguished in this series. There exist several other types which are not represented in the series. This clinicopathologic classification, in addition to the previously mentioned features, is helpful in predicting the prognosis of a particular case.

A scatter diagram (Fig. 2) combining anatomical stage and histologic grade of malignancy is of definite value in classifying bladder cancer, as well as selecting a technique for treatment of each type of bladder cancer. In addition, the tumor should be evaluated as primary or recurrent and categorized as to clinicopathologic type.

2. THE SMALL CENTRAL SOURCE OF RADIUM OR COBALT 60

Radium. A 25 mg. radium capsule, filtered with 0.5 mm. Pt and having an active length of 1.0 cm. and an external diameter of 2.3 mm. was used in most cases (Fig. 7).

The unavailability of a point source of radium which could provide truly spherical isodose surfaces of radioactivity was at first deplored. An automatic isodose recorder was constructed[6] and the isodose surfaces of radiation from linear radium sources studied (Fig. 8). Fortunately, the shape of these surfaces best conformed to the contour of an average bladder and vesical neck and to the oblate spheroid (tangerine) shape of the inflated balloons (Fig. 14). The larger size of the linear radium source, compared with a tiny cobalt 60 pellet, makes it easier to handle, especially at the operating table when its position inside the catheter must occasionally be altered to suit the tumor (Fig. 16). Radium is preferable when a two-capsule tandem must be used for a large elliptical tumor (Fig. 19) or in the posterior urethra (Fig. 17 and 18). The automatic isodose recording of the tandem source forms a prolate spheroid, whereas farther away it forms

TABLE I

CLASSIFICATION AND RESULT ACCORDING TO CLINICAL TYPES

Type	Number Dead	Number Alive	Survival Time (in Years) for Each Patient
Papillary Cancers			
Grade 1, multiple lesions	0	3	5, 6, 6
Grade 2, single lesion	—	8	3, 3, 5, 6, (with disease), 7, 7, 8, 9
Grade 2, multiple lesions	2	6	2, 4, 4, 5, 6, 10
Grade 2, bulky extensive lesion	1	0	———
Grade 2, diffuse papillomatosis	1	1	3 (cystectomy after radiation failure)
Infiltrating Cancers			
Single lesion	4	2	3 (with disease), 9
Multiple nodular lesions	2	2	2, 9 (with recurrent disease)
Bulky lesion with perivesical extension and infiltration	6	2	3, 5
Extensive, widespread, superficial infiltration	2	1	6
Postresection prophylactic radium	0	1	5
With prostatic infiltration	3	2	6, 8
Sarcoma	1	0	———

FIG. 7. Central sources. Radium and cobalt 60 sources employed in the Walter Reed technique. The topmost source is the 25 mg. radium capsule. Beneath it is a somewhat bulky encapsulated cobalt 60 source. This has been discarded. The next source, opposite #4, is the favorite cobalt 60 source. It is a cylinder 1.0 mm. in diameter and 1.0 mm. high, encapsulated in monel metal. The initial activity was 20 mc. The 2 round cobalt sources at the bottom are the cobalt beads. These are not encapsulated (see Figure 10). To the right of the radium is the wire basket employed to fix the radium in position in the catheter. To the right of this is a paper clip for comparison of size.

FIG. 8. Isodose surfaces of the radium source constructed with the aid of an automatic isodose recorder. Note how the contours of the isosurfaces resemble those of the vesical neck.

a sphere (Fig. 9). Balloon catheters having these shapes are available (Fig. 15).

On rare occasions, when a sensitive bladder cannot tolerate a radium balloon for four days, the 25 mg. radium source is replaced with a 100 mc radon source and each treatment lasts one day instead of four.

Cobalt 60 Pellets. After considerable experimentation, two types of radioactive cobalt 60 pellets were designed and finally standarized (Fig. 7, 10 and 11). The specifications entailed a source narrower than the lumen of the central channel of the catheter so as not to obstruct the flow of urine, and sufficiently small so as to act as a point source and yield spherical isodose surfaces.

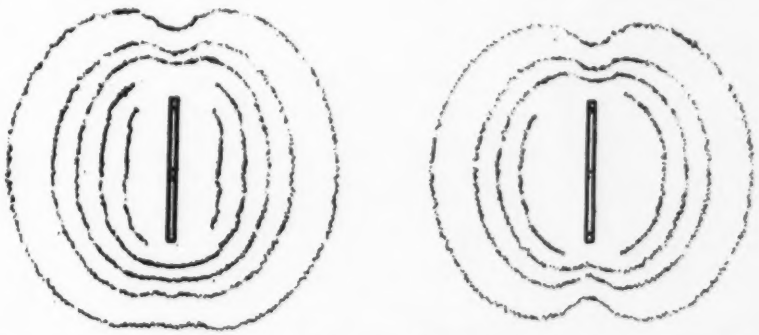

FIG. 9. Automatic isodose recordings of two radium capsules in tandem alignment. Active length per capsule is 1.5 cm.; filter 1.0 mm. Pt. On the left, the "eye" ends of the capsules are arranged in series. On the right, the "eye" ends are on the outside. Depending on the radium-surface distance, these may be inserted into prolate spheroid or spherical balloons (Fig. 15).

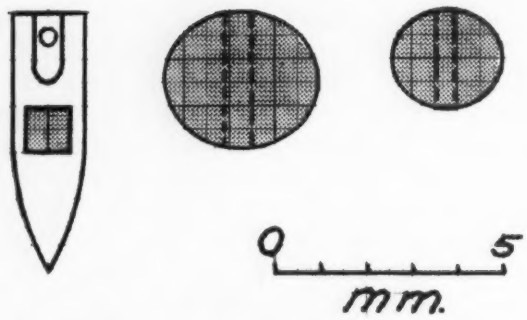

FIG. 10. Diagrammatic illustration of the three radioactive cobalt sources. The one on the left is the 1.0×1.0 mm. encapsulated cylinder. The other two are beads; they are not encapsulated.

One pellet, constructed by the Canadian Atomic Energy Commission plant is a 1.0×1.0 mm. cylinder of radioactive cobalt 60 having 20 mc activity. It is encapsulated in a steel sheath, pointed at one end and having an eye at the other end for threading. Its external measurements are 5.0 mm. length and 1.6 mm. diameter (Fig. 10 and 11).

Two sources constructed by the Oak Ridge Institute for Nuclear Studies were radioactive cobalt alloy beads, almost spherical in shape and measuring 2.2 and 3.3 mm. in diameter, respectively. They have a central hole for threading. Only the smaller bead has been used for bladder cancer. The alloy hardens the pellet and minimizes flaking. The strength is also approximately 20 mc (Fig. 10 and 11).

Radioactive Solutions. Several radioactive isotopes in solution have been tried by others: gold, sodium, bromine, and finally cobalt. The first three sources, as would be

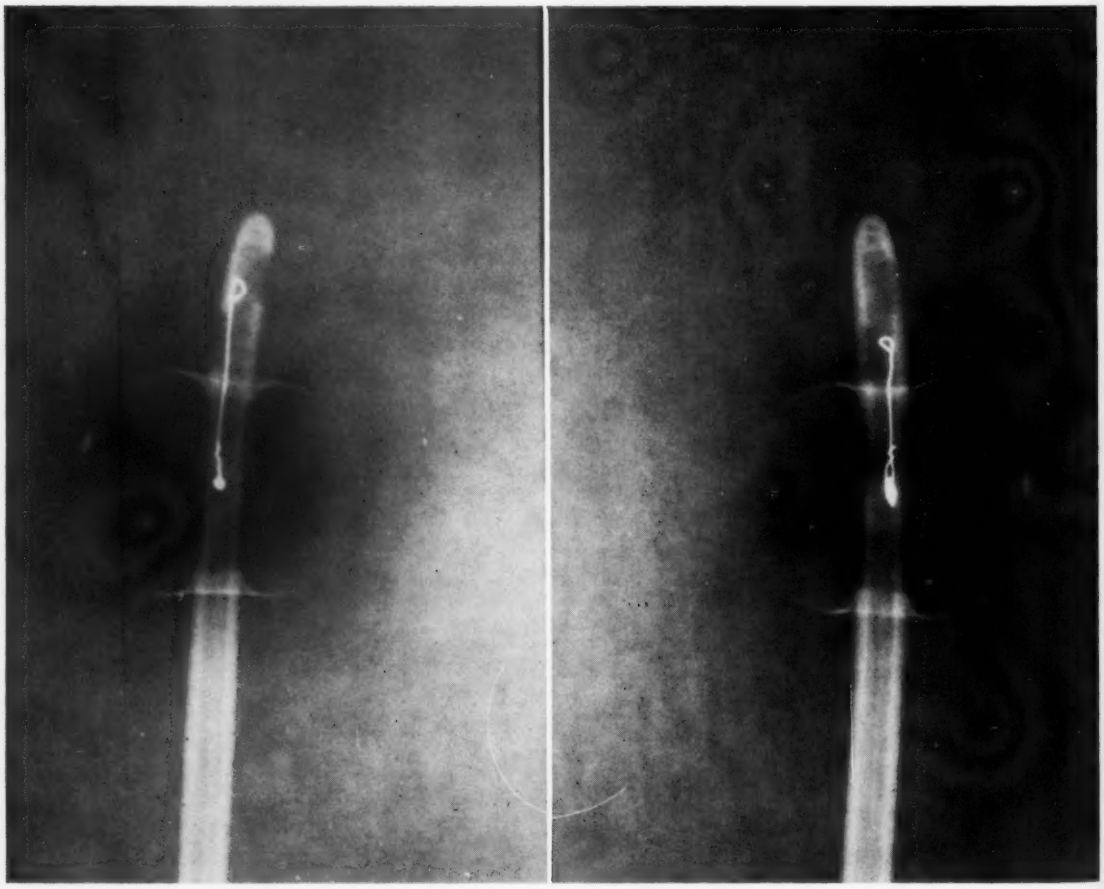

FIG. 11. Method of fastening cobalt 60 bead and cylinder inside the central channel of a catheter, with the aid of piano wire, looped at both ends, and sutured at the upper end with silk to the wall of the bladder. The one on the left is a threaded bead; on the right is the encapsulated pellet.

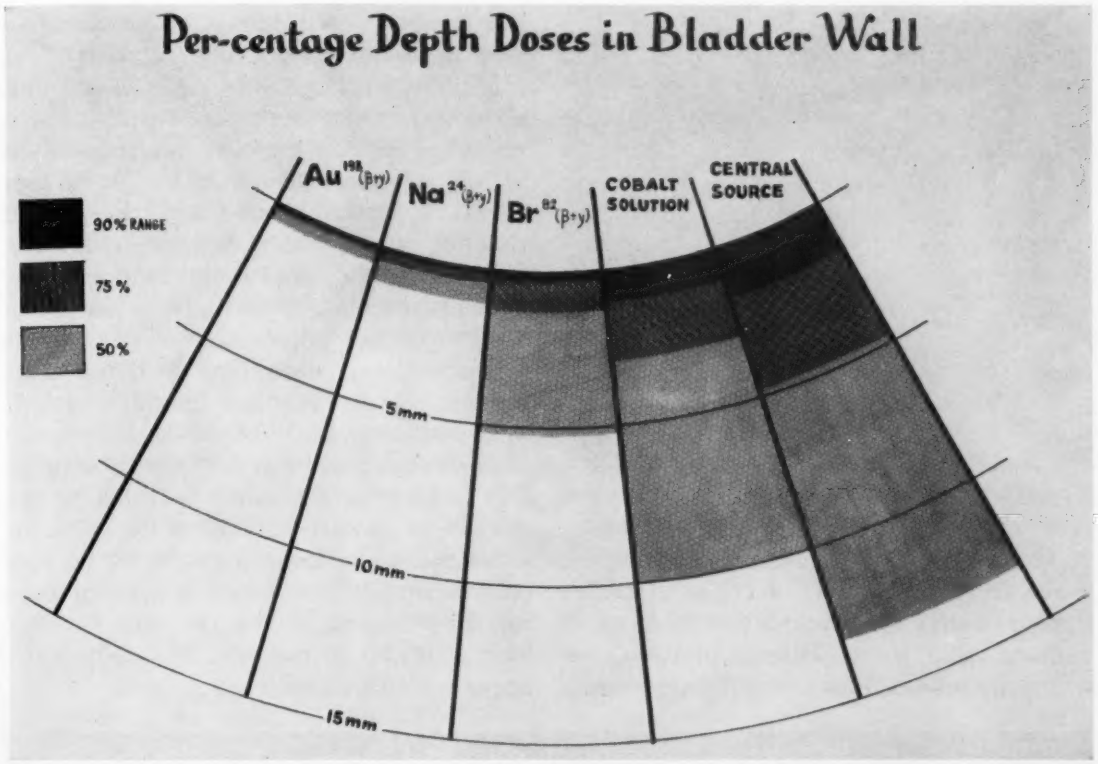

Fig. 12. Diagrammatic illustration of the percentage depth doses in the bladder wall from different types of sources. The first four segments illustrate the effect of various radioactive isotope solutions. Radioactive gold and sodium deliver cauterizing doses of beta rays to the epithelium of the bladder mucosa only and are not at all effective in treating carcinoma. Radioactive bromine is only slightly more efficient. Cobalt solution is more efficient than the other isotopes. In the last column are indicated the percentage depth doses from a central source of radium or radioactive cobalt. At a depth of 1.0 cm., the central source delivers 33 per cent higher depth dose than the cobalt solution. At this critical point which commonly represents the deepest portion of the tumor, the difference in percentage depth dose may be decisive between cure and failure.

expected theoretically, yielded inefficient percentage depth doses while giving intense cauterizing surface doses (Fig. 12). Cobalt solution, as used by Muller,[5] was better, but did not yield as good a depth dose as a central source. For example, at 1.0 cm. from the surface of the balloon, a central source yields 33 per cent greater depth dose than cobalt solution (Fig. 12). This significant difference at a critical depth is often decisive between cure or failure.

Cobalt solution was first tried[5] because it produced homogeneous isosurfaces of depth doses, regardless of the asymmetry of the inflated balloon. Previously, using a central source, we quickly solved the problem of the asymmetric balloon by throwing it away and using only a symmetric one. Now symmetric balloons are easily procurable for the Walter Reed technique. The central source is preferable to cobalt solution because of: higher percentage depth dose; greater simplicity in preparation of the applicator; minimal exposure to the radiotherapist; absence of dangerous exposure to the patient when the balloon breaks; ease of rearrangement of size or shape of balloon, or change of the position of the source when the location or geometry of the tumor is unusual; ease of fractionating dosage because the technique is not cumbersome —a critically important feature; and finally, a central source does not have the undesirable beta rays of cobalt solution which serve only to burn the surface of the bladder unduly.

One potentially fruitful exception for a radioactive solution lies in the treatment of multiple papillomatosis by the direct instillation of a solution of Au^{198} into the bladder. The theoretic considerations of this technique are sound, and the dangers of contamination are being reduced, according to Ellis.[4]

Ultimately, the results will determine which is the most efficient technique. To date, our technique has achieved a 56 per cent five-year apparent arrest rate. This is a high goal for others to aim at and for ourselves to reproduce.

3. SUITABLE BALLOON APPLICATOR TO IRRADIATE THE LOWER TWO-THIRDS OF THE BLADDER

The technique is designed to irradiate the *lower two-thirds* of the bladder because: approximately three-fourths of all bladder tumors occur there. Tumors of the dome are easily removed by segmental resections. Furthermore, symptoms of cystitis are more readily tolerated if only part of the bladder is irradiated. In cases where cystostomy has not been performed, a reservoir of urine can form in the upper third of the bladder, which then drains out of the suprapubic tube and the central channel of the Foley catheter (Fig. 20). Otherwise, it has been found that the urine distends the bladder and pushes the tumor away from the balloon. If a cystostomy is performed, as is desirable, the dome of the bladder is pulled into a cone shape with its apex at the stoma, thus preventing contact with the balloon, however large it may be. The hypersensitive cancerous bladder can tolerate a smaller balloon of 40 to 50 cc. volume for the lower two-thirds, but usually is unable to tolerate a larger balloon for the required length of time. Furthermore, with larger balloons, adequate drainage is difficult to achieve.

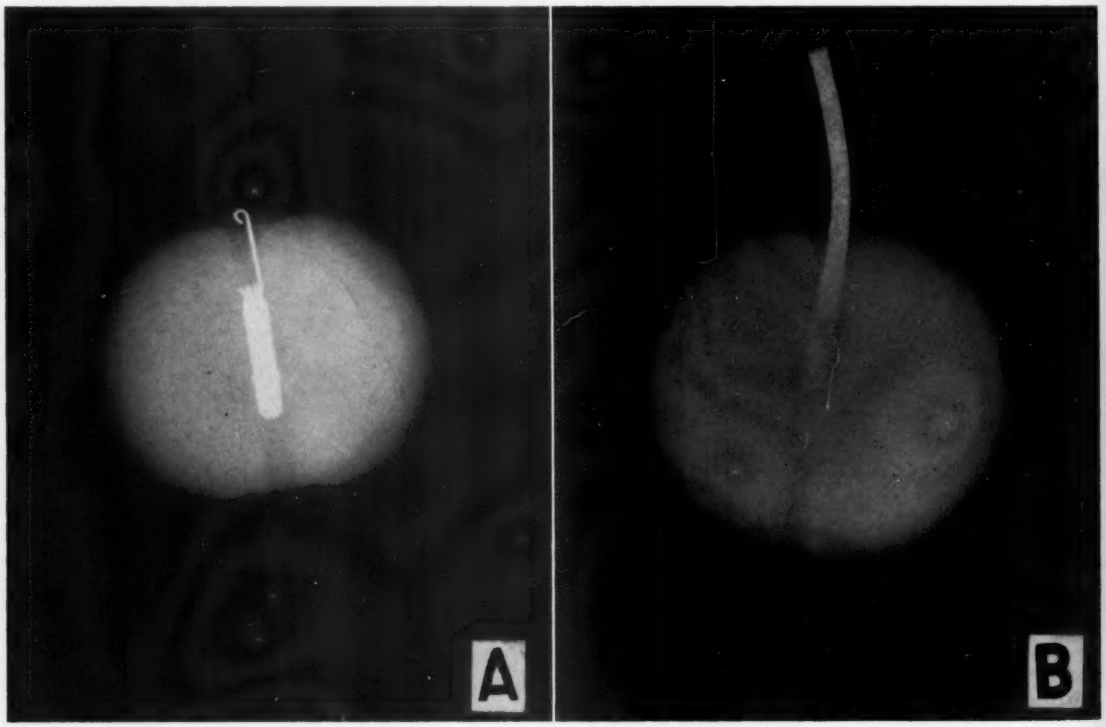

FIG. 13. (*A*) Twenty-five milligram radium capsule inside a wire basket which is sutured with silk to the wall of the catheter. (*B*) Another method of fixing the radioactive source in the balloon. A piece of ureteral catheter is cut to the distance from inside the tip of the catheter to the radium or cobalt capsule. Nylon or linen threads from the latter are run through the ureteral catheter and out through the tip, with the aid of a needle, and tied.

The most frequently employed catheter is the standard Foley two-channel catheter, F 26 guage, with a 30 cc. balloon, the lumen measuring 4.0 mm. in diameter. When the radium (2.3 mm. diameter) or cobalt pellet (1.6 mm. diameter) is fixed in the catheter, urine will drain freely alongside either radiation source. If a narrow urethra cannot be dilated, an F 24 catheter is used, the lumen measuring 3.6 mm. in diameter. The overinflated balloon (40 to 45 cc. solution in a 30 cc. balloon) has the shape of an oblate spheroid (Fig. 14). Special catheters are available, the balloons of which inflate to form a sphere or a prolate spheroid.

Formerly, the catheter was modified by cutting off the tip (Fig. 15). However, in several instances, the urine did not drain freely through the single orifice, or the bladder dome would collapse against the opening and obstruct free drainage. The authors prefer a two-channel catheter with two holes in the tip and a third hole below the balloon (Fig. 15).

Fixation of the Source inside the Catheter. In order to fix the source inside the catheter, a special wire basket was designed to hold the radium (Fig. 7 and 13*A*). The capsule slips through the four-pronged, spring-like wires and rests inside the basket without additional fixation. After the bas-

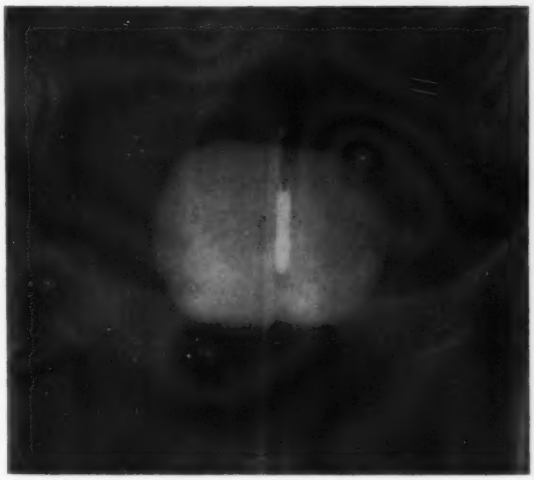

Fig. 14. Prolate spheroid balloon of 30 cc. capacity, overdistended with 45 cc. dilute sodium iodide solution. The radium-surface distance is 2.2 cm. This is the most commonly employed applicator.

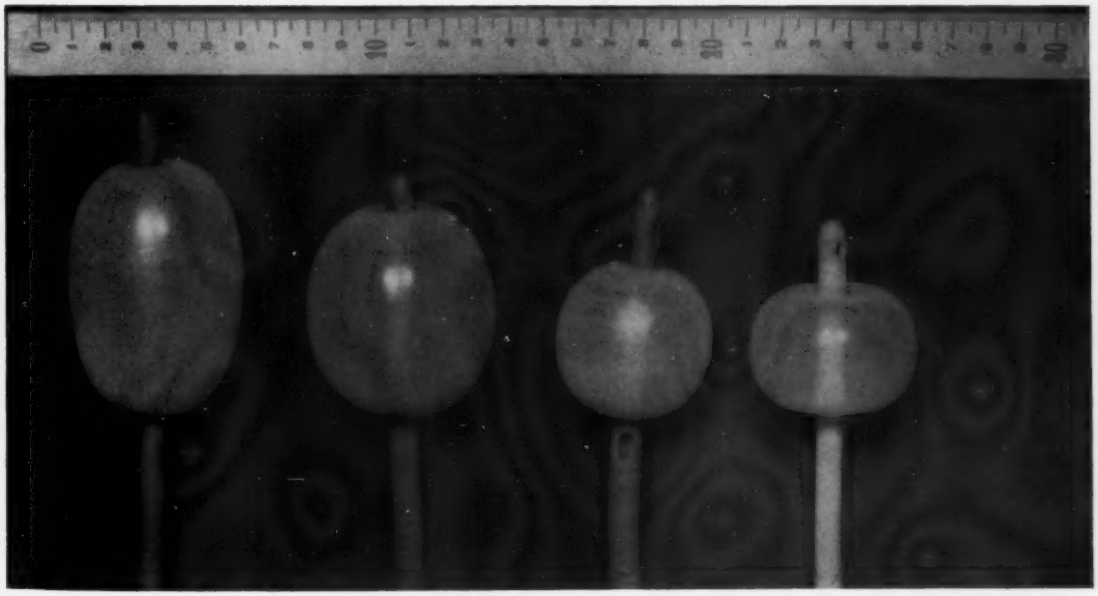

Fig. 15. Four types of balloons used to contain a central source. The most popular balloons are on the right. They are 30 cc. balloons overinflated with 40 to 45 cc. solution. The oblate spheroid shape is consistent with the isosurfaces from a linear radiation source the active length of which is 1.0 cm. Note the secondary drainage hole below the balloon. The short (whistle) tip on the second balloon from the left is not used any more because the bladder mucosa often contracts on it and blocks urine drainage. Note the third drainage hole beneath the balloon, second from the right.

ket is inserted in the large channel of the catheter, the small loop at the upper end of the wire can be seen through one of the orifices at the tip of the catheter and is sutured with silk to the wall of the catheter.

Another equally efficient method of fastening the radiation source in the center of the balloon is by making a loop at both ends of a piece of piano wire. One end is threaded through the eye of the radium capsule or cobalt pellet and the other end is sutured with silk to the wall of the catheter (Fig. 11).

Still another method for fixing the radioactive source in the drainage tube of the Foley catheter is to use a portion of a ureteral catheter cut to the distance from the inside of the tip of the catheter to the "eye" end of the capsule, when the center of the radioactive source is positioned in the center of the balloon (Fig. 13*B*). Threads of nylon or linen are passed on a straight needle from the eye of the radium capsule, through the lumen of the ureteral catheter, and through the tip of the Foley catheter, and tied. The piece of ureteral catheter acts as a spacer, which fixes the radium in position, while at the same time allowing urine to drain through the central channel.

Positioning of the Source inside the Catheter. Originally, the radiation source was always placed in the center of the balloon. On several occasions, inspection of the balloon's position in the bladder through the cystotomy wound showed that the tumor lay cephalad to the radium. The position of the radium was then adjusted so as to lie at the same level as the tumor (Fig. 16). On the other hand, when the tumor was at the vesical neck or infiltrated the prostate, the radium was moved to the appropriate lower position. With the radium in the latter position, the large tissue doses delivered to the prostate and posterior urethra were well tolerated by the patient, probably due to total destruction of the sensitive nerve ends in the posterior urethra. Furthermore, the normal prostate can tolerate large doses of irradiation.

A recurrence in the posterior urethra can be irradiated by suturing the radium capsule in appropriate position below the balloon (Fig. 17). Due to the short radium-tissue distance, three 25 mg. capsules left in position for one hour will provide a total exposure of 75 mg. hr., which delivers

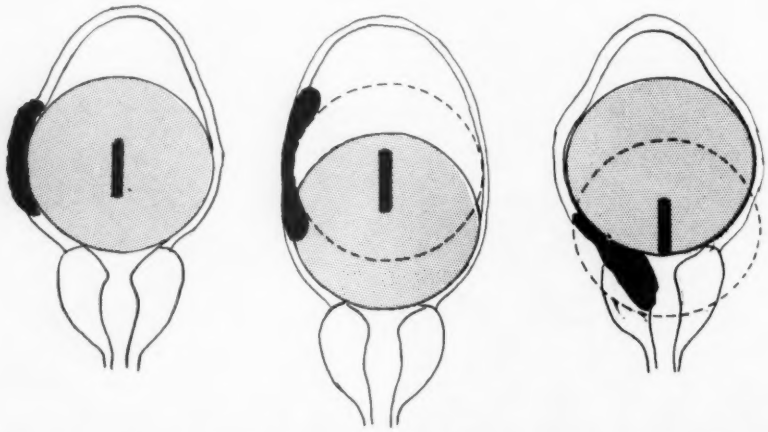

FIG. 16. Modification of position of the radium to suit the demand of the tumor. On the left the radium is in correct position with respect to the tumor. In the middle diagram, after the balloon was inflated, it was found that the tumor had extended higher than the balloon. The radium was moved to an upper position in the balloon and its isosurface now corresponded with the tumor. The diagram on the right illustrates a common lesion of the vesical neck which infiltrates the prostate. The radium is moved to a lower position whereby its isosurfaces will effectively irradiate the tumor. Two lesions of this type were successfully destroyed more than five years ago. Only when cystotomy is performed at the time of radium insertion can errors of this type be discovered and corrected.

a tissue dose of approximately 1,000 r_γ at a distance of 4.0 mm. from the source. Since the exposure time is short, no attempt to insure urine drainage during the treatment is necessary. When tumor is present in both the bladder and posterior urethra, a 25 mg. capsule can be placed in the center of the balloon and a radium needle of 2.0 mg. content below the balloon (Fig. 18). This applicator produces the same roentgen flux in the posterior urethra and bladder while permitting free urine drainage during the treatment.

4. CYSTOTOMY SUPERVISION DURING RADIUM INSERTION

Although the catheter with the radiation source is inserted through the urethra, it is desirable at the same time to open the bladder from above for seven important reasons. Bulky tumors can be shaved down by electrosurgery or conservatively resected and the wound edges sutured. Blank gold radon seeds may be implanted around the tumor for subsequent roentgenographic inspection (Fig. 25). If the balloon is not in proper contact with the tumor it can be inflated further or replaced by a different shape balloon. If necessary, the position of the radium can be altered inside the balloon (Fig. 16). A two-capsule radium tandem in a prolate spheroid balloon may be inserted if indicated (Fig. 19). Most importantly, the cystostomy is the best method for assuring effective urine drainage from above while there is additional drainage through the urethral catheter (Fig. 20). Finally, symptoms of cystitis due to acute postirradiation epithelitis are

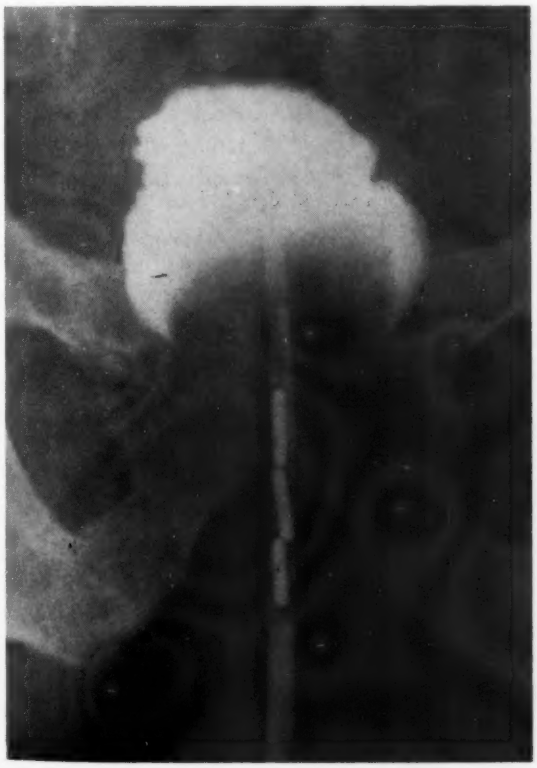

FIG. 17. Position of three-capsule tandem in the posterior urethra. The carcinoma in the bladder had been destroyed at a previous treatment. The balloon is inflated with water. Sodium iodide was injected through the catheter for the purpose of studying the contour of the bladder wall.

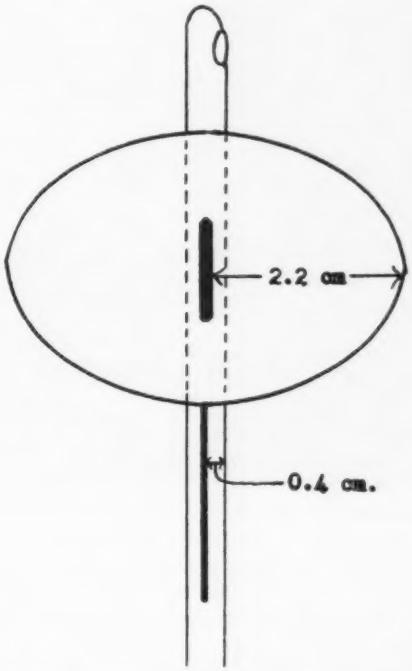

FIG. 18. Applicator used for papillary carcinomatosis with lesions in the bladder as well as the posterior urethra, similar to Figure 31*A*. The central source was 25 mg. radium, active length of 1.0 cm., and distance of 2.2 cm. In seven days an exposure of 4,200 mg. hr. delivered a tissue dose of 7,000 r_γ. The urethral source was a 6.0 mg. needle, active length of 2 cm., and distance of 0.4 cm. It was left in place for only sixty hours, so that an exposure of 360 mg. hr. delivered a surface dose of 9,000 r_γ.

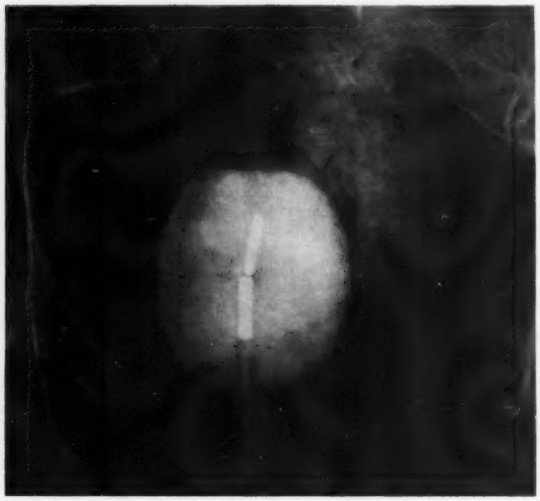

FIG. 19. Arrangement of 2 radium capsules in tandem for an elliptic tumor. This applicator was constructed at the operating table when cystotomy inspection indicated that the standard single capsule in a balloon was inadequate (see Case VI, Fig. 30*A*).

minimized if urine drains freely through the stoma for a few weeks after the radium treatment.

In this series of 50 cases, cystotomy was performed 35 times. The increased precision in the application of the radiation source probably contributed materially to the high five year arrest rate.

Although we stated above that, at cystotomy, bulky papillary tumors could be coagulated almost down to their base, it has been found that immediate radium treatment of the unhealed ulcer retards healing and often produces an unduly painful cystitis. It is therefore recommended that, for papillary carcinoma, electrocoagulation be performed several weeks prior to the radium insertion so that the defect can heal. If the tumor protrudes only slightly into the bladder cavity, coagulation is undesirable, as it is helpful to have tumor tissue available for mid-treatment serial biopsy.

If a papillary carcinoma can be regionally resected and the wound edges sutured, the area can tolerate subsequent radium application more comfortably than can a bladder having a recent electrocoagulation ulcer. This type of local resection prior to radium has also been performed successfully on infiltrating cancer (see Case 5 in original article[1]).

It has been difficult to communicate to other therapists the importance of cystotomy, because of the understandable desire to avoid an operation which seems to them unnecessary. The tangible and intangible benefits plus the high arrest rate resulting from this surgical procedure far outweigh the disadvantages of possible wound implants (3 cases in this series), longer hospitalization and increased morbidity.

5. ROENTGENOGRAPHIC CONTROL DURING TREATMENT

Two major sources of error in any balloon technique are: incorrect position of the radiation source with respect to the tumor, or displacement of the tumor by the accumulated urine. Roentgenographic examination should be undertaken promptly after radium insertion. This consists of intravenous pyelography, or cystography with a small amount of contrast medium introduced into the bladder by gravity, depending on the conditions of treatment and the status of the patient. Occasionally, for clearer observation, sodium iodide solution in the balloon is first replaced with water (Fig. 20).

This control may disclose different types of unsuspected technical errors. The catheter must occasionally be pulled down and

FIG. 20. Appearance of radioactive cobalt pellet inside the balloon catheter in a patient. Sodium iodide introduced by gravity through the cystostomy showed the balloon to be in good apposition to the tumor of the vesical neck.

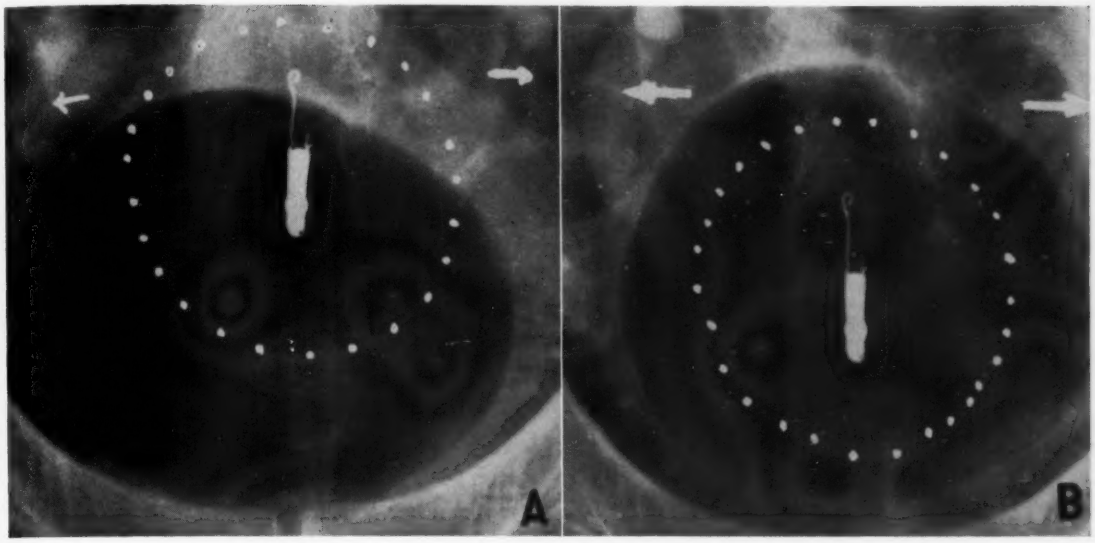

Fig. 21. (*A*) Contrast medium from intravenous pyelography collecting in the vesical neck because balloon floated up toward the dome. (*B*) Traction on the catheter fixes the balloon against the base of the bladder.

fastened to the thigh in a semi-taut position, so that the balloon cannot rise out of the vesical neck (Fig. 21, *A* and *B*). Another error is illustrated in Figure 22, in a patient with diffuse bulky papillomatosis, involving the entire bladder mucosa. A cystogram during treatment (Fig. 22) demonstrated poor approximation of the bladder wall to the tumor, due in part to tenting of the dome from previous cystotomy adhesions. In this case a dose of 8,032 r_γ in seventeen days had very little effect on the tumor (Grade 2—Stage B_1), and a cystectomy, performed several months after the radium insertion, has kept the patient alive without evidence of cancer for five years. Figure 23 illustrates a recurrent infiltrating carcinoma of the left wall and adjacent trigone (Grade 3—Stage

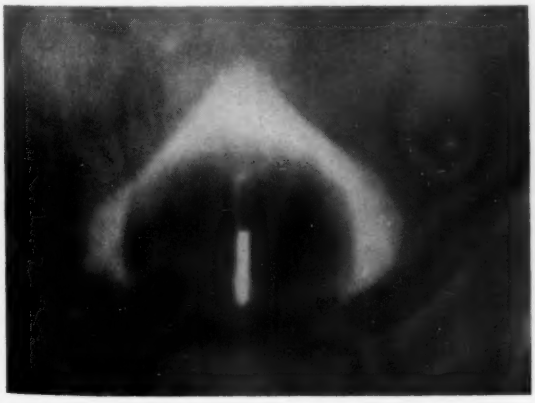

Fig. 22. Cause of failure. A previous cystotomy produced adherence of the dome of the bladder to the abdominal wall. For undetermined reasons urine collected bilaterally pushing the bladder wall and the tumor away from the balloon.

Fig. 23. Expedient utilization of asymmetry. This was an infiltrating extensive Stage C carcinoma of the left lower portion of the bladder which had excavated a crater. Even though urine drainage was somewhat unsatisfactory, the balloon fitted well into the crater and was retained in position. The primary tumor was completely destroyed. The patient died three years later of remote metastasis.

FIG. 24. Complication which could have been avoided if cystotomy had been performed. Hemorrhage from the vascular tumor was activated by the insertion of the balloon applicator. Blood clots pushed the tumor away from the balloon. This was promptly corrected.

C), wherein previous cystotomies rendered another operation inadvisable. The intravenous cystogram disclosed a symmetric balloon inside an asymmetric bladder cavity. Since there was excellent apposition of the balloon to the tumor, it was not changed. The local result was excellent. The patient died three years later of distant metastasis, but with no carcinoma in the bladder. Another source of error occurs when blood clots displace the bladder wall (Fig. 24); in which event, the balloon is removed temporarily in order to clean out the bladder.

Figure 25 illustrates blank radon seeds, inserted cystoscopically to outline the tumor. In the absence of cystostomy, the poorly draining urine collected between the balloon and the tumor. In this instance, the catheter was replaced with one having a larger channel. Figure 26 illustrates another patient in whom cystotomy was not performed. The cystogram, made with an excessive amount of contrast medium, disclosed a previously unsuspected diverticulum, though the radium balloon was against the tumor. Treatment was completed. Two years later, a new tumor occurred in the unirradiated diverticulum. Had the radium originally been inserted under cystotomy supervision, steps could have been taken to circumvent the difficulty.

Each roentgenographic examination entails multiple views and should be repeated as often as necessary.

FIG. 25. An intravenous pyelogram demonstrating faulty urine drainage, due to a small blood clot in the central channel of the catheter. This was removed by simple syringe irrigation. The dummy radon seeds delineate the tumor. They had been inserted cystoscopically, as the bladder was not opened.

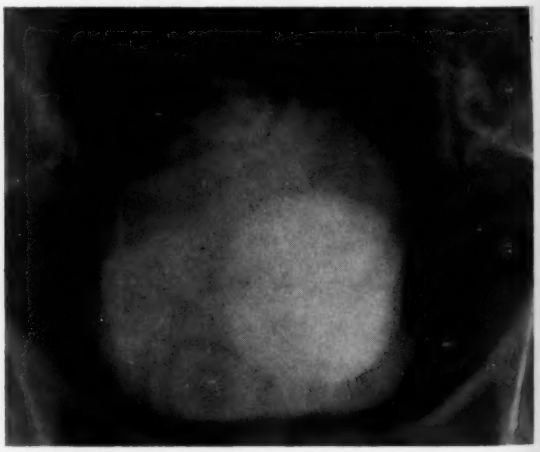

FIG. 26. This cystogram was made with an excessive amount of fluid and disclosed an unsuspected diverticulum. Radium treatment was completed. However, two years later, a new tumor appeared in the diverticulum. This might have been circumvented if cystotomy had been performed at time of radium insertion.

6. FRACTIONATION

The Walter Reed technique usually requires two radium treatments of approximately four days each, with an interval between treatments of five to seven days (Fig. 30); occasionally, the interval has been as long as twelve days.

The most common balloon applicator, with a 25 mg. radium capsule at 2.2 cm. distance, delivers a daily dose at the surface of the balloon of approximately 1,000 r_γ. The first of the two radium sessions delivers a dose of 4,000 r_γ in four days. After an interval of five to ten days, the radium is re-inserted for an additional two to six days to complete a total dose of 6,000 to 10,000 r_γ. Occasionally, for an early papillary carcinoma, the entire dose is given in one session. Thus, the over-all time may range from six to twenty days. The advantages of this fractionation are self-evident.

Immediately prior to the second radium insertion, cystoscopic inspection of the tumor yields some evidence of the response to the first dose of 4,000 r_γ. A shrinkage of 25 per cent in tumor volume at this early date usually indicates favorable response. Another favorable observation is the reduction of irregular, nodular, raised granulations to a flat denuded crater or shallow ulcer, which may be covered by a pseudodiphtheritic membrane. This type of clinical evidence was helpful in about one-third of the cases.

In 3 cases of moderately advanced, bulky infiltrative tumors, the cystotomy wound was reopened at the time of the second radium treatment to permit more careful inspection of the effect of the first radium dose. In all instances the alteration in the shape of the tumor-bearing area was so marked that the second radium treatment was changed in design and dosage to fit the new requirements. These 3 bladders were cleared of cancer. Two of the patients are alive for three and five years, respectively.

7. SERIAL BIOPSY AT SECOND RADIUM TREATMENT

At the time of the second radium insertion, cystoscopic inspection reveals the gross response to the first 4,000 r_γ. This is a useful guide in estimating the degree of radiosensitivity in one-third of the cases. It is made more exact by a biopsy and rapid paraffin section made within twenty-four hours. This type of clinical and histologic analysis helps determine the second dose to be delivered.

The transurethral punch biopsy yields very small pieces of tissue which are sometimes inadequate for the histologic evaluation of irradiation effect. In 3 critical cases, the cystotomy wound was re-opened at the time of the second radium insertion and a large piece of tissue excised for histologic study.

Serial biopsies were performed on 20 patients in this series (see Table II). In 14 cases the biopsy specimen presented an accurate histologic picture of the effect of the first dose of radium. In 6 cases, the biopsy specimens were unsatisfactory or the histologic study yielded inaccurate information.

Certain types of histologic changes are significant. If an undifferentiated carcinoma, Grade 4, (Fig. 5*A*, Case VI) shows marked acute cell death,[4] the tumor can be considered radiosensitive (Fig. 5*B*, Case VI) and will require a minimal tumor lethal dose of 6,000 r_γ in approximately two weeks.

Another favorable type of histologic re-

TABLE II

EVALUATION OF 20 SERIAL BIOPSIES

	Accurate	Inaccurate
Cases where histologic response was called favorable and patient survived more than three years	12	
Cases where histologic response was poor, and irradiation failed	2	
Cases where histologic interpretation was incorrect		4
Biopsy specimen unsatisfactory		2
Total	14 (70%)	6 (30%)

sponse occurs in papillary carcinoma, Grade 2. A dose of 4,000 to 5,000 r_γ will change a solidly cellular cord or island of tumor cells (Fig. 3*A*) to a papillary stalk almost denuded of cancer cells but covered with normal radioresistant transitional epithelium showing slight radiation changes (Fig. 3*B*). Isolated areas are seen containing disintegrating cancer cells, the viability of which cannot be definitely ascertained (Fig. 3*C*). These may be responsible for recurrence. Case VIII is a slightly different type of papillary carcinoma, Grade 2 (Fig. 31*B*). Irradiation destroyed most of the tumor except for a few residual islands of degenerating tumor cells deep in the muscularis (Fig. 31*C*).

A radioresistant variety of bladder cancer is a Grade 2 papillary carcinoma which has become infiltrating Grade 3 (Fig. 4*A*). This may show little or no response to radium, especially if the tumor is bulky and with a broad base (Fig. 4*B*). Another variety of Grade 3 carcinoma consists of articulating islands and cords of infiltrating, moderately undifferentiated carcinoma (Fig. 6*A*, Case V). This tends to be radiosensitive (Fig. 6*B*, Case V).

In general, serial biopsies should be performed whenever possible. They often contribute data which materially aid in the treatment of a patient. The authors now believe that they should have been performed in more cases. In a number of instances, complete fulguration of the tumor prior to the radium treatment prevented serial biopsy studies. Great care should be taken to remove deep-seated tumor tissue for study, since histologic interpretation is impossible if the specimen is not representative.

8. THE TOTAL DOSE

After classification of the original tumor, the total dose is empirically estimated. This may be modified after mid-treatment inspection and serial biopsy study. The total dose is dictated by the demands of the tumor, but must be as small as possible to minimize radiation cystitis.

In order to obtain enough cases to illustrate the range of dosage employed in this series, the total doses given to the three-year survivors are presented in a scatter diagram (Fig. 27).

One group of patients was treated in a single session lasting five or six days with doses ranging from 5,500 r_γ to 8,300 r_γ. These were small papillary carcinomas or feeble patients who could not tolerate two treatments. In these cases, dose selection was empirical as there was no interim inspection or serial biopsy.

The range of tumor lethal dose for bladder cancer is broad. The most common dose was 8,000 r_γ in ten to seventeen days. The largest successful dose was 11,000 r_γ in fifteen days. Four radioresistant tumors failed to respond to doses of approximately 10,000 r_γ.

Small doses are well tolerated by the bladder. Large doses may cause severe cystitis. A study of Figure 28 illustrates this feature. There are many paradoxical observations. Three bladders had only mild reactions with doses of 10,000 r_γ. This is due in part to the fact that, with the central source technique, only two-thirds of the bladder is irradiated.

All doses discussed herein represent the exposure dose at the surface of the balloon. In most instances, when the technique is accurate, the dose at the mucosal surface of the bladder is identical with that at the surface of the tumor. If a tumor is thick, the surface dose must be increased in order to deliver a tumor lethal dose to the deepest portion of the tumor (see Case VI and Fig. 30*C*).

SUPPLEMENTARY FEATURES

Radiation Cystitis. This painful complication is influenced by many predictable and unpredictable factors. A sensitive bladder prior to treatment usually succumbs to a severe radium reaction. Minimal disease in the bladder is attended by a minimal reaction. Minimal postfulguration scarring of a bladder is attended by a minimal reaction. Following extensive fulguration, it is often wise to defer radium application for one or two weeks until the

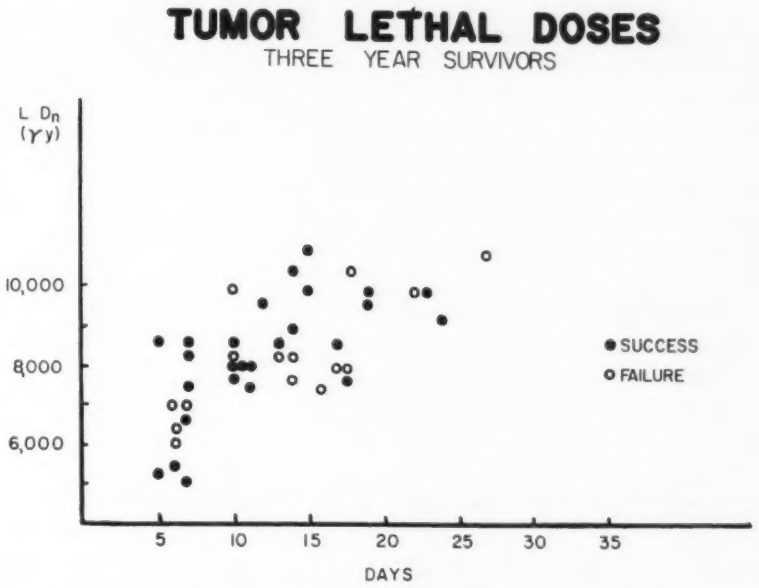

FIG. 27. Illustration of total tumor doses employed in this series. The solid dots represent patients who survived more than three years. The circles represent failures. Note that there were 4 failures in spite of surface doses of approximately 10,000 r_γ. One group of patients was treated with a single long exposure lasting five or six days. The tumor doses in this group ranged from 5,500 to 8,300 r_γ. When two courses were employed, the over-all time ranged from ten to twenty-five days.

infection has abated and the ulcer healed to some extent.

Radium treatment, following segmental resection, is well tolerated. On two occasions, in order to avoid the cystitis that ensues when a fresh coagulation ulcer is immediately irradiated, the tumor was locally resected, the wound sutured and the radium balloon immediately inserted. In both instances the incision in the bladder healed without complication and the radium cystitis was mild.

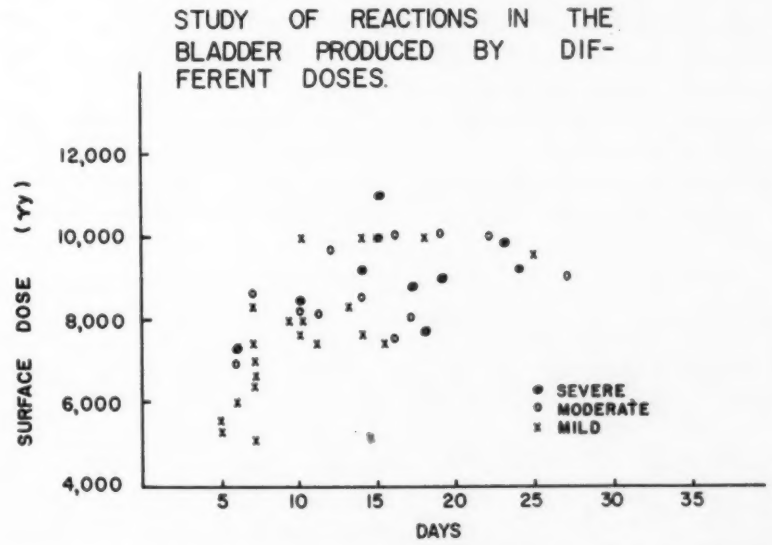

FIG. 28. Study of radium-induced cystitis. The unpredictability of this complication is manifested by the fact that 3 patients with doses of 10,000 r_γ had mild cystitis. In general, the larger the dose, the more intensive the cystitis. A bladder with pain and urinary frequency before radium application is more prone to develop severe cystitis than an asymptomatic bladder.

The incidence of radium cystitis in this series is illustrated in Figure 28. A "mild" reaction signifies no discomfort or slight discomfort and frequency of urination. A "severe" reaction signifies dysuria and frequency of urination every fifteen minutes to one hour for six months or more. A "moderate" reaction lies between the two.

There is a relation between dose and cystitis. Severe reactions did not occur with doses less than 7,500 r_γ. Paradoxically, there were 4 instances of mild cystitis following large doses between 9,000 and 10,000 r_γ. On the other hand, 5 patients had severe reactions with doses between 7,000 and 8,000 r_γ.

Three types of reactions are of consequence: those occurring during treatment due to the balloon applicator acting as a foreign body; radium mucositis occurring one month after treatment and usually transient; and late dysuria and frequency of urination due to a persistent infected ulcer or fibrotic contracture of an irradiated bladder.

Severe pain during treatment due to the foreign body in a sensitive bladder can be controlled with analgesics, morphine if necessary. When the latter failed, we replaced the 25 mg. radium capsule with a capsule containing 100 mc radon in order to shorten the duration of the exposure and discomfort. The pain was neutralized by frequent injections of morphine.

Tables III and IV give the incidences of early and late radium reactions.

TABLE III

RADIUM REACTIONS ONE MONTH AFTER TREATMENT

r_γ	Mild	Moderate	Severe
11,000		1	
10,000	3	1	1
9,000	1	2	3
8,000	1	1	3
7,000	5	1	3
6,000	3		
5,000	2		
Total	15	6	10

TABLE IV

LATE RADIUM REACTIONS (THREE TO SIX MONTHS)

r_γ	None	Mild	Moderate	Severe
11,000				1
10,000	1	2	1	1
9,000	1	1		2
8,000	5	2	1	1
7,000	5	2		2
6,000	3			
5,000	1	1		
Total	16	8	2	7

It may be said that a severe early reaction is prone to be followed by a severe late reaction. A severe late reaction is commonly accompanied by a fibrotic contracted bladder, pale mucosa, urinary frequency every one-half to one hour, and a bladder capacity of 50 to 120 cc. The intensity of the late reaction is dependent more on the sensitivity of the bladder and the individual idiosyncrasy rather than the size of the dose.

Failures. Seven patients who died had no residual carcinoma of the bladder. Three died of distant metastasis, 3 of heart failure, and 1 of gastric hemorrhage two weeks after treatment. This suggests that the technique is more efficient than the results indicate. However, the numerous cystoscopic and operative procedures and the prolonged radium treatment exert a strain on the whole body which may on occasion overstrain the heart. The technique is attended not only by morbidity, but also mortality.

In 9 instances there was residual disease in the irradiated area (Table v).

Some failures were probably due to faulty technique, chiefly, improper urine drainage resulting in displacement of the tumor from the balloon. Other failures were due to undue thickness of the tumor resulting in inadequate dosage to the remote portion of the tumor. In general, a radioresistant tumor thicker than 1.5 cm. should not be treated. On the other hand, a radiosensitive tumor as thick as 2.5 cm. will

Table V

FAILURE OF THE TECHNIQUE

(residual disease or recurrence in irradiated area)

Papillary Tumors	Infiltrative Tumors
r_γ	r_γ
8,322 (bulky tumor)	8,345
7,750 (bulky tumor)	10,000
8,366	10,500
7,000 (prostate involved)	
8,032 (extensive tumor)	
7,518	

flatten during treatment, so that toward the end of irradiation the remote portions of the tumor will be close to the radium applicator.

Recurrences in the Bladder Dome. The Walter Reed technique cannot be properly used to irradiate the dome of the bladder. Fortunately, most bladder cancers occur below the dome. However, in this series, new tumors appeared later in the dome in 6 patients. Two of three papillary carcinomas were successfully treated, 1 by coagulation and 1 by resection. Of the 3 infiltrating lesions, 1 recurred six and one-half years later and remained under control for three more years; the other 2 patients died. Of the 6 recurrences, 3 occurred in patients who had cystotomy and 3 in patients without cystotomy.

Thus, recurrence in the dome is one of the weaknesses of the technique. It is acceptable as a calculated risk in view of the over-all favorable arrest rates. Furthermore, the recurrence can be countered surgically on occasion.

Abdominal Wound Implants. There were 3 instances of abdominal wound implants in 35 cystotomies. All were highly malignant infiltrating cancers. Only 1 was arrested with intensive irradiation (Fig. 30*B*).

This is another risk which is acceptable in view of the numerous advantages gained by cystotomy and the ultimate good results.

RESULTS

In order that any treatment technique may be properly evaluated, its achievements must be determined according to the extent of the tumor and degree of malignancy. Therefore, the results will be reviewed for each category. One measure of the efficiency of a treatment technique for bladder cancer lies in the number of infiltrating cancers it can arrest. In this respect it may be useful to discuss the seven infiltrating carcinomas (Grade 3 and 4) arrested for more than five years.

Infiltrating Cancers Arrested More Than Five Years

Case I. Grade 3—Stage B_1. In this patient there were 3 papillomata and 1 nodular mass 1 cm. in diameter above the right ureteral orifice in 1946. The diagnosis was papillary carcinoma with early infiltration. The patient is free of disease for nine years. Illustrated in original paper.[1]

Case II. Grade 4—Stage C. In 1946, a 1.5×3.0 cm. sessile tumor on the anterior bladder wall was segmentally resected in this patient. The excision line was close to the tumor. It was a highly undifferentiated carcinoma, histologic Grade 4, which had infiltrated the serosa. Radium therapy was instituted one week after operation. Patient is free of disease and symptoms for nine years. Illustrated in original paper.[1]

Case III. Grade 3—Stage B_2. This patient, in 1946, had 2 firm nodular recurrent masses on and above the trigone, both palpable vaginally. The diagnosis was undifferentiated carcinoma with squamous cell metaplasia. The patient remained free of disease for eight years. Now, in the ninth year, she has an extensive recurrent mass in the dome of the bladder. Illustrated in original paper.[1]

Case IV. Grade 3—Stage C. In this patient there was, in 1947, a large infiltrating carcinoma of the vesical orifice, 5 cm. in diameter, involving the entire right half of the vesical neck and infiltrating deeply the right lobe of the prostate. The tumor was excised, the base fulgurated and then irradiated. Patient is free of disease for more than ten years. Illustrated in original paper.[1]

Case V. Grade 3—Stage C. A.S., female, aged sixty years, was first irradiated on April 9, 1949 for an extensive mucosal and submucosal carcinoma with 3 independent infiltrating nodules (Fig. 29). The first course of radium application entailed a surface dose of 4,360 r_γ in four days. On the eighth day, cystoscopic

examination showed a pseudodiphtheritic membrane covering almost the entire lower bladder where the superficial excoriation had been present. It was estimated that there was 40 per cent clinical shrinkage. Biopsy (Fig. 6*B*) disclosed marked tumor destruction. Because the tumor was not unduly thick, a total surface dose of 8,168 r_γ was delivered in eleven days. A moderately severe cystitis followed which abated in two months. Cystoscopic examination six years later showed no evidence of disease or late radiation scarring. The patient is now asymptomatic and her urine is clear.

Comment. This flat, extensive, superficial type of infiltrating carcinoma constitutes an ideal indication for the Walter Reed technique because the bladder wall is not rigidly indurated and accommodates itself to the shape of the bag. A similar lesion in another patient was somewhat more radioresistant, although the serial biopsy suggested a favorable response. The lesion recurred in spite of the same dose and caused death of the patient.

CASE VI. Grade 4—Stage D_1. A.T., male, aged fifty-two years, had primary advanced infiltrating carcinoma of the upper posterior bladder wall, measuring 3.0×5.0 cm. in diameter and about 2.5 cm. thick (Fig. 30*A*). At cystotomy, on January 5, 1950, the posterior wall of the bladder was found to be fixed due to extravesical extension. It was evident that a conventional balloon catheter would provide unsatisfactory radium distribution. Therefore, a prolate spheroid balloon with a two-capsule tandem was employed (Fig. 19). The first radium treatment entailed a surface dose of 4,240 r_γ in four days. Because of the atypical applicator, it was decided to observe its effect carefully and the cystotomy wound was re-opened on the tenth day for the second radium treatment. The tumor had shrunk 25 per cent in size. A punch biopsy was made and the radium reinserted. The biopsy specimen (Fig. 5*B*) showed marked radiation effect. The lesion was radiosensitive, but in order to properly irradiate the outlying part of this thick tumor, a total surface dose of 10,507 r_γ in fourteen days was given (Fig. 30*C*). The subsequent cystitis was mild in spite of the large dose.

Five months after the first radium treatment, there appeared a 7.0 cm. diameter, deeply situated, abdominal wall implant (Fig. 30*B*). A skin dose of 7,200 r in thirty days was delivered through a 10×10 cm. portal with 250 kv. roentgen rays. The tumor dose ranged from 3,300 to 6,700 r. The shrinkage was incomplete, and consequently 16 radon implants of 1.5 mc each were inserted. The exposure of 3,200 mc hr. delivered a tissue dose of 5,740 r_γ. There ensued a radiation ulcer which required five years to heal.

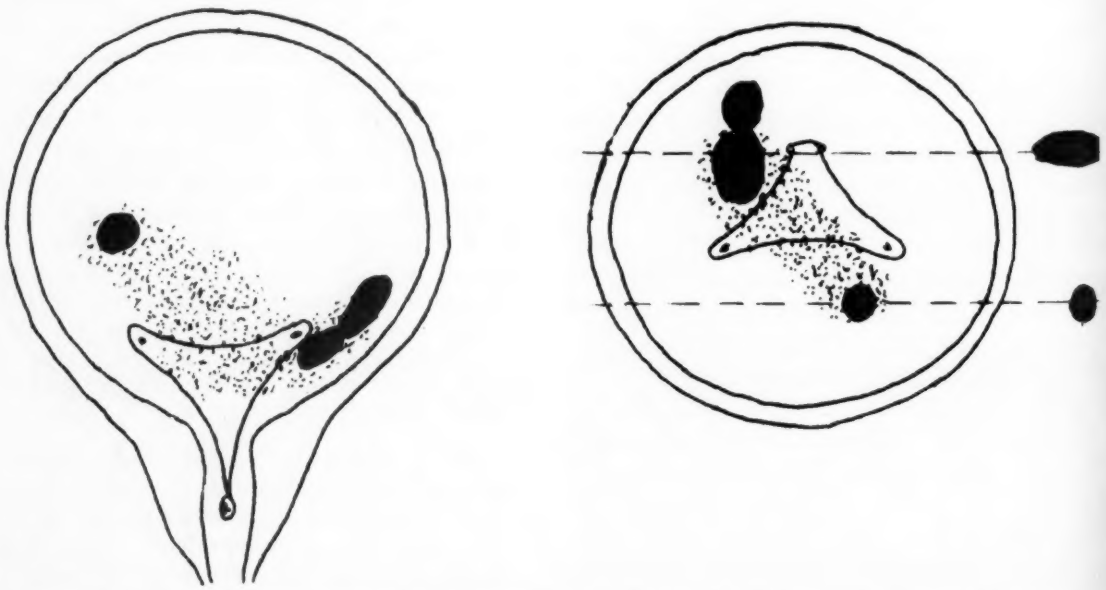

FIG. 29. Case v. Undifferentiated carcinoma, Stage C, Grade 3 (see Fig. 6). In addition to the 3 nodules of infiltrating carcinoma, the intervening excoriated mucosa (stippled area) was also invaded by carcinoma.

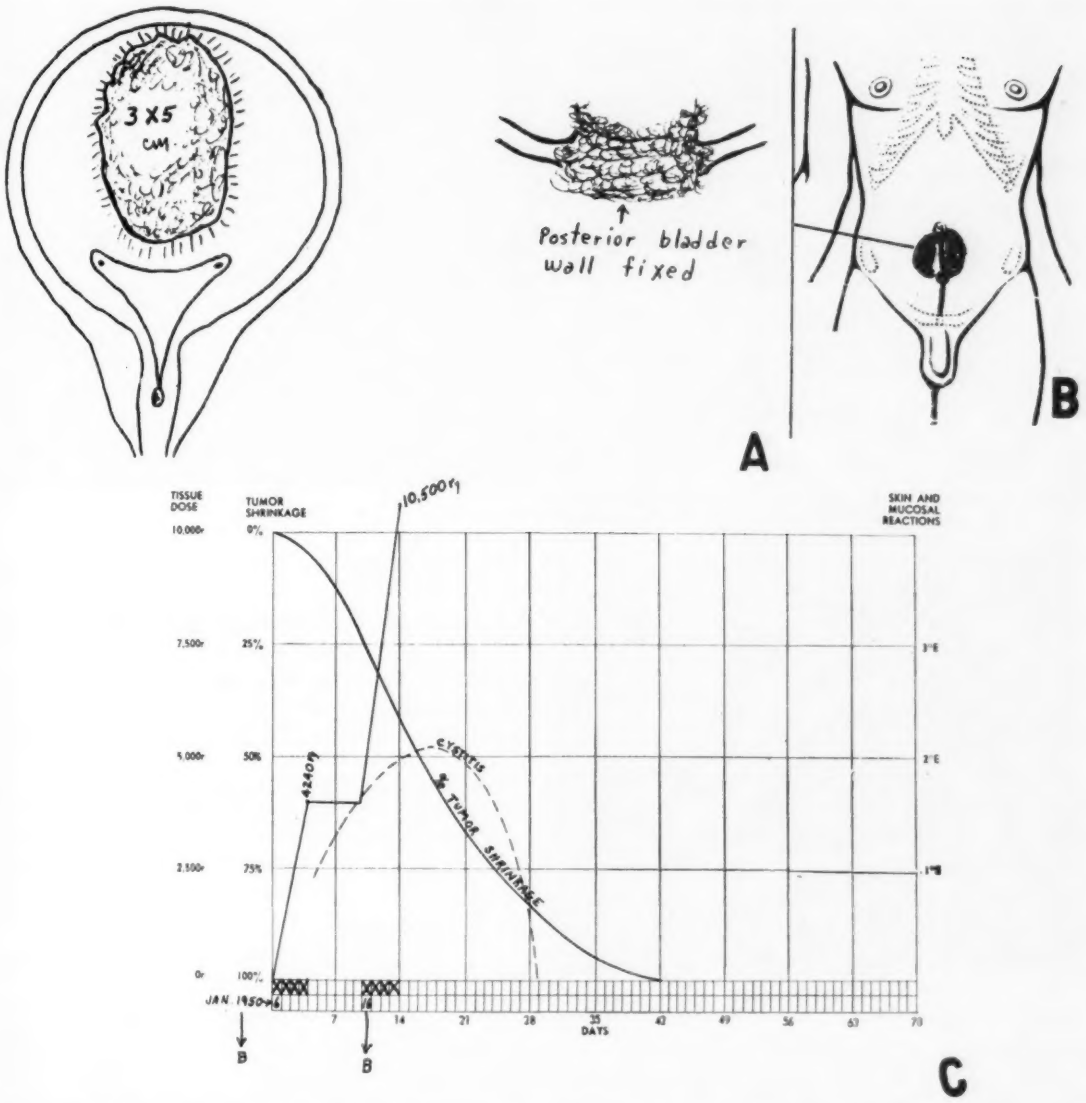

FIG. 30. Case VI. (*A*) Undifferentiated carcinoma, Grade 4 (see Fig. 5). Tumor extended through posterior wall, fixing it in the pelvis. Classified as Stage D_1 because of abdominal wound implant. (*B*) Wound implant, 7.0 cm. in diameter and extending down to bladder. Controlled with roentgen therapy and radon insertion. (*C*) Treatment chart. Lesion arrested seven years.

During all this time, the patient remained in excellent health, had no bladder symptoms, and on cystoscopic examination there was only a slight fibrous scar at the site of the former tumor.

Comment. This unusual seven year survival of an advanced highly malignant carcinoma with extravesical extension and large abdominal wall implant is evidence that some carcinomas of the bladder are extremely radiosensitive. This case strongly supports the opinion that undifferentiated carcinoma of the bladder should be treated by irradiation rather than surgery.

CASE VII. Grade 3—Stage C. In 1949 this patient had a swelling over the right half of the vesical neck which extended into the sphincter. It resembled an edematous convoluted bulging mucosa and covered the right lobe of the prostate. A large portion was removed by transurethral resection. Two weeks later, massive uncontrollable hemorrhage necessitated emergency cystotomy and radium therapy. A depressed crater lined with pink granulations was

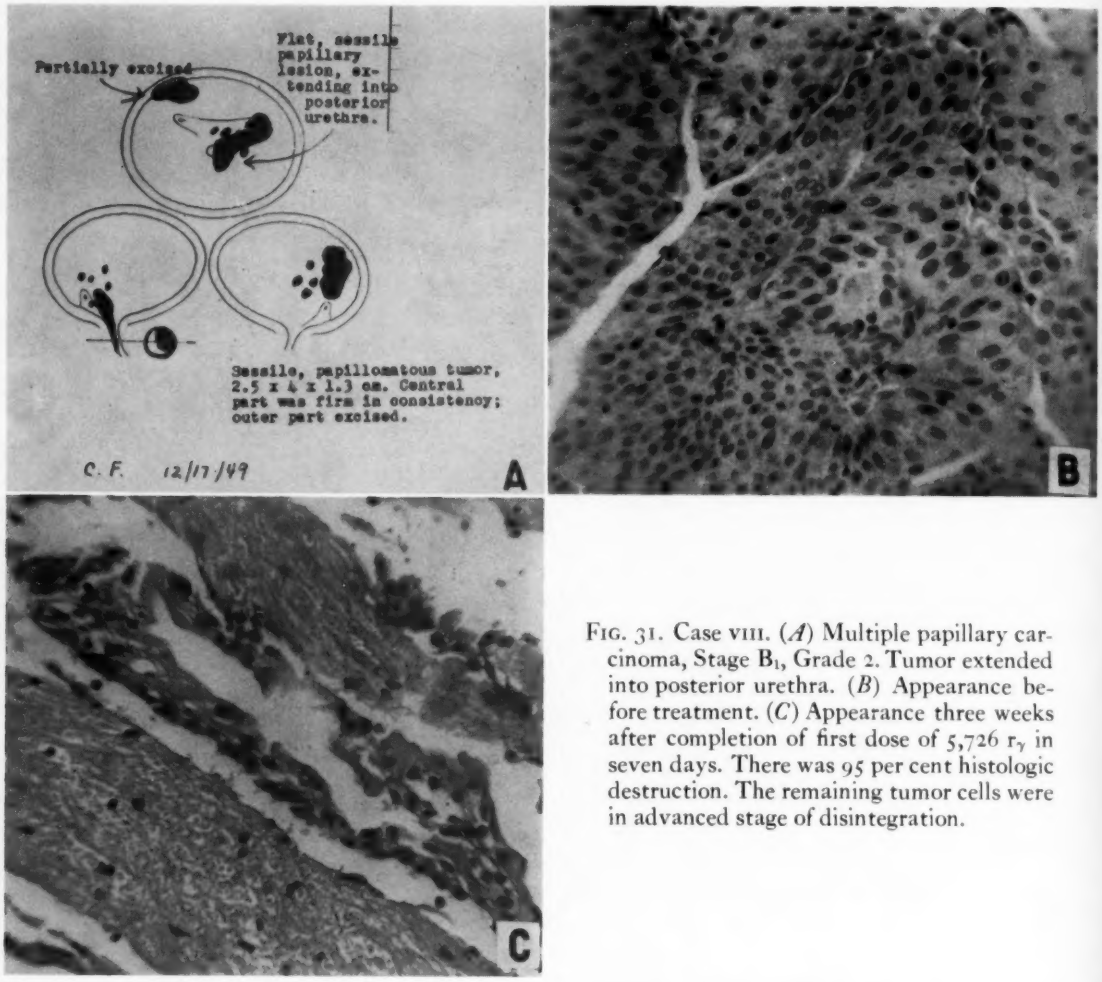
Partially excised
Flat, sessile papillary lesion, extending into posterior urethra.
Sessile, papillomatous tumor, 2.5 x 4 x 1.3 cm. Central part was firm in consistency; outer part excised.
C. F. 12/17/49
A
B
C

FIG. 31. Case VIII. (*A*) Multiple papillary carcinoma, Stage B_1, Grade 2. Tumor extended into posterior urethra. (*B*) Appearance before treatment. (*C*) Appearance three weeks after completion of first dose of 5,726 r_γ in seven days. There was 95 per cent histologic destruction. The remaining tumor cells were in advanced stage of disintegration.

found on the right wall of the vesical neck and extending into the bladder. There was free bleeding from all parts of the crater. Radium was applied. The patient is now free of disease for seven years.

A Case of Multiple Papillary Carcinoma

CASE VIII. C.F., male, aged fifty-eight years, was first irradiated December 16, 1949 for multiple papillary and sessile tumors, Grade 3—Stage B_1 (Fig. 31*A*). The largest lesion bordered the left margin of the trigone and extended into the posterior urethra. The lesion on the right wall of the bladder was partly excised (Fig. 31*B*). A large, 50 cc. balloon was overdistended with 80 cc. of fluid so that the radium-tissue distance was 2.5 cm. The first course of treatment delivered a surface dose of 5,726 r_γ in seven days. There was an early, moderately severe, reaction and cystoscopy one week after the radium therapy revealed a spastic bladder with 30 cc. capacity. The second radium treatment was therefore deferred. On the twenty-first day, cystoscopy disclosed a 50 per cent clinical shrinkage. Histologically, there was marked destruction of the tumor; more than 95 per cent of the tumor cells disappeared. The remaining tumor cells showed an advanced stage of disintegration (Fig. 31*C*). Therefore a total dose of 9,216 r_γ in twenty-four days was given. The cystitis was moderately severe for three months and thereafter it gradually improved. Five years later the bladder had a capacity of 250 cc. and caused no symptoms.

Comment. This patient's bladder was able to tolerate the large balloon so that the centrally placed radium apparently effectively irradiated the entire bladder wall. The large surface dose of 9,216 r_γ was

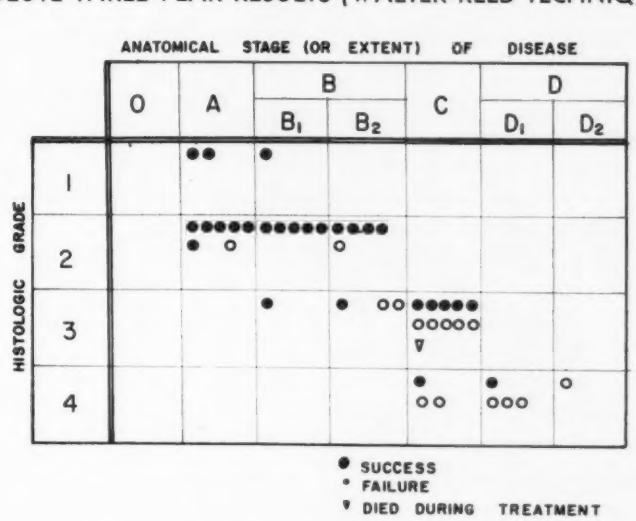

FIG. 32. Three year apparent arrests according to each classification. There were 46 patients, and 22 were free of disease. The three-year *absolute apparent arrest rate* was 54 per cent. Note the large number of arrests of early cancer and the significant achievement in infiltrating cancer.

selected in order to deliver a tumor lethal dose at the dome of the bladder and to the region of the posterior urethra.

Statistical Compilation

The three-year and five-year apparent arrest rates are presented in scatter diagrams (Fig. 32 and 33). A greater percentage of papillary tumors (Grades 1 and 2) were arrested than infiltrating tumors (Grades 3 and 4), which is to be expected since the papillary tumors are less virulent than the infiltrating lesions. However, it is noteworthy that, of 16 infiltrating tumors,

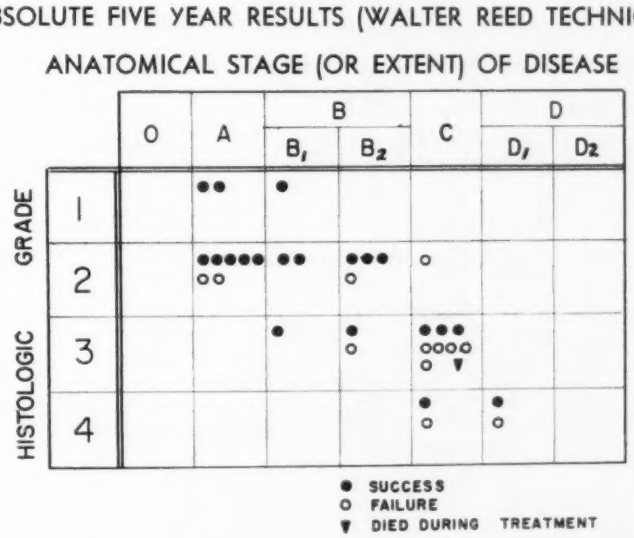

FIG. 33. Five year apparent arrests according to each classification. There were 34 patients, and 19 were free of disease. The five-year *absolute apparent arrest rate* was 56 per cent. Note that in Stages C and D_1, there were 5 arrests, and that there were 7 arrests of infiltrating cancers. Also note the few failures in papillary cancer, Grades 1 and 2.

TABLE VI

RESULTS IN 50 CASES OF BLADDER CANCER TREATED WITH THE WALTER REED TECHNIQUE FROM 1945 TO 1953

	Number of New Cases	Years Free of Cancer									
		1	2	3	4	5	6	7	8	9	10
1945	1	1	1	1	1	1	1	1	1	1	1
1946	5	5	5	5	5	5	3	3	3	3	
1947	4	3	3	3	3	3	3	3	3		
1948	3	1	1	1	1	1	1	1			
1949	14	11	8	6	6	6	6				
1950	7	6	5	4	3	3					
1951	7	4	3	3	3						
1952	5	3	2	2							
1953	4	4	3								

SUMMARY OF RESULTS

Years after Treatment		1	2	3	4	5	6	7	8	9	10
No. of cases treated	50	50	50	46	41	34	27	13	10	6	1
Number alive		38	31	25	22	19	14	8	7	4	1
Per cent alive		76	62	54	53	56	51	60	70	66	100

7 (45 per cent) were arrested for five years. From the standpoint of clinical staging, there were 12 Stage C cases (perivesical extension), of which 4 (33 per cent) were arrested for more than five years.

A compilation of all cases in this series is

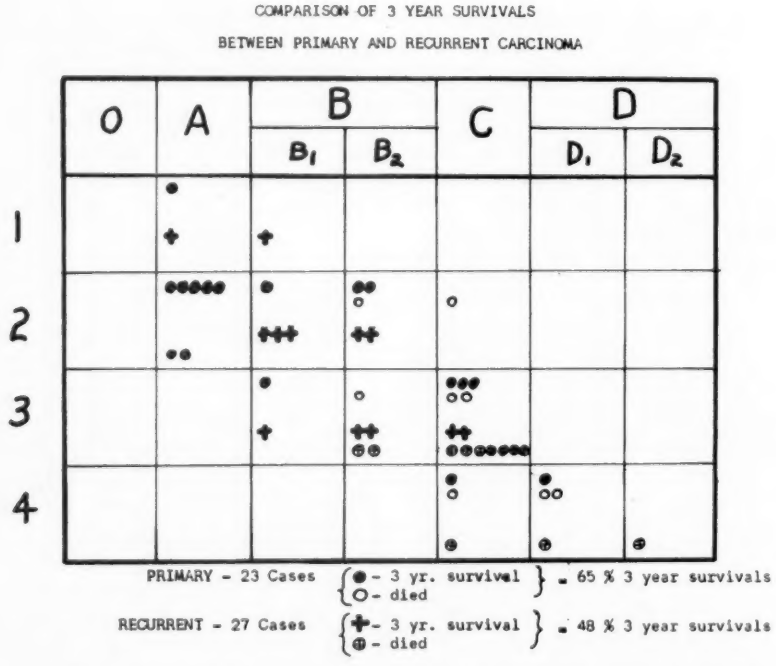

FIG. 34. Comparison of three-year survivals in primary and recurrent carcinoma.

given in Table VI. Fifty patients were treated between 1945 and 1953. These are absolute figures of all patients treated. Thirty-four patients were treated more than five years ago. Their apparent arrest rate was 56 per cent. This unusually high rate will not be maintained because, although 11 of the first 12 lesions were arrested more than five years, the subsequent results were poorer in spite of increased experience and technical proficiency.

Comparison of Prognosis between Primary and Recurrent Tumors

In order to examine this feature, the three-year arrest rates were studied (Fig. 34). The three-year arrest rate for primary cancer was 65 per cent, and for recurrent cancer 48 per cent. There was no significant difference between the papillary and infiltrating tumors.

CONCLUSIONS

1. The Walter Reed technique for bladder cancer entails a small central source of radium or cobalt 60 in a proper balloon catheter irradiating the lower two-thirds of the bladder. It is an elaborate technique necessitating the flexible application of eight basic principles to the requirements of each type of tumor.

2. Success depends on meticulous technique backed by judgment.

3. Substitution of various radioisotope solutions, that fill the entire balloon, for a central source is much less efficient, with the possible exception of cobalt 60 solution. Physically, the latter is somewhat less efficient than the radium and has other disadvantages.

4. Bladder cancer occurs in many clinicopathologic types. A standard treatment technique cannot be employed for all categories. Results of any technique must be independently evaluated for each category of bladder cancer. A scatter diagram combining the anatomical stage and histologic degree of malignancy is helpful in classifying bladder cancer.

5. In a series of 50 patients treated between July, 1945 and April, 1953, the absolute five-year apparent arrest rate was 56 per cent.

6. Primary tumors yield better results than recurrent tumors (65 per cent as compared with 48 per cent three-year arrests).

7. There are two weaknesses in the Walter Reed technique: a proneness toward recurrences in the dome (6 cases) and abdominal wound implants (3 cases). Some of these recurrences can be arrested with surgery or fulguration. These detractions are minimal compared with the ultimate high arrest rates.

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LATE RESULTS OF RADIATION THERAPY FOR CANCER OF THE CERVICAL STUMP*

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SINCE the description, by Chrobak[3] in 1896, of cancer occurring in the retained stump of the uterine cervix, much has been written and discussed concerning the treatment of this serious disease. Early reports of results of treatment were so pessimistic that much argument was advanced for always performing total hysterectomy instead of the more usual subtotal hysterectomy for benign disease of the uterus. With the impressive improvement in surgical skill in recent years, the risk of death from total hysterectomy is little more than that from subtotal hysterectomy, though Meigs[8] has warned of the increased morbidity. He has discussed the possibility of injury to the ureters and bladder, and the chance of vaginal prolapse and foreshortening of the vagina. On the other hand, any operation less extensive than total hysterectomy does not prevent the future occurrence of cancer in the retained cervical stump; Meigs has pointed out that cautery to the cervix, coning out of the cervix, or trachelorrhaphy had not forestalled the appearance of cancer in the stump in some of his patients.

Radiation therapy has been the accepted treatment for cancer of the cervical stump. The poor results reported in early years were soon ascribed to treatment of already existing cancer following an incomplete operation for benign or malignant disease of the uterine corpus, leaving an unrecognized cancer in the retained cervical stump. This distinction was recognized by Sharples[10] and by Nuttall and Todd;[9] these authors considered that if at least two years had elapsed between surgical treatment and discovery of the cancer in the stump, one was dealing not with an overlooked malignant lesion but with a true case of cancer of the stump. Nuttall and Todd called the overlooked cases, in which less than two years had elapsed between operation and diagnosis, "coincident cases," and the ones in which diagnosis had been made more than two years after operation, "true cases." Later authors[1,4] have observed this distinction. Results of treatment in coincident cases have continued to be poor, as would be expected with any incomplete operation for cancer; results in true cases have shown marked improvement.

Whether subtotal hysterectomy, with its lessened morbidity, should be totally abandoned in favor of total hysterectomy would seem to depend in part on the incidence of cancer in the retained stump of the cervix. This is a difficult figure to arrive at, since few patients operated on for uterine myomas, pelvic inflammatory disease, or menorrhagia are followed for many years. Estimates vary considerably; the incidence of carcinoma of the stump in comparison with the number of cases of cancer of the cervix is usually 4 per cent or more. The incidence of cases of carcinoma of the stump obtained by follow-up of patients who had undergone supravaginal hysterectomy for nonmalignant uterine disease is considerably lower, averaging around 1 per cent of cases.[2,7,11] Insistence on total hysterectomy, with its slightly higher mortality and morbidity, would also seem to depend on the results of treatment of cancer

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of the cervical stump. If, following subtotal hysterectomy on 1,000 patients, cancer of the cervical stump will later develop in 10 or more of them, what is the chance of cure with careful treatment? General surgery has made encouraging progress in the last few decades, and so has therapeutic radiology. Early reports showed few cures; studies in more recent years have been much more encouraging.[1,4]

EARLIER RESULTS

During the years 1915 through 1930, 1,676 patients with cancer of the uterine cervix were treated with radium therapy at the Mayo Clinic;[5] of this number, 108 (6.4 per cent) had cancers of the stump of the cervix. Of the 108 patients, 99 were treated with radium and supplemental roentgen therapy; 57 (approximately 58 per cent) of the 99 had true cancers of the stump diagnosed two years or more after subtotal hysterectomy, compared with 42 (42 per cent) of coincident cases. Five-year survivals among the true cases numbered 15 (26.3 per cent) of the total; of the coincident, 9 patients (21.4 per cent) survived for five years or more. The extent of the lesions is of interest: in the true cases only 20 per cent were Stage I or II, and 80 per cent were Stage III or IV; of the coincident cases, only 3 (7 per cent) were Stage II, and the remainder were Stage III or IV.

THE PRESENT STUDY

Since the five-year salvage in this early group was so low, we thought a more recent study advisable. The period chosen was January 1, 1940, through December 31, 1949. During this ten-year span 1,451 patients who had carcinoma of the cervix were seen at the clinic, including 98 patients who had cancer of the cervical stump, an incidence of 6.8 per cent, almost identical with the incidence of the earlier study. Here the similarity ends; 84 (approximately 86 per cent) of the 98 fell into the category of true stump cancers, leaving only 14 (about 14 per cent) as coincident cases. The occasion for the subtotal hysterectomy had been a fibromyoma in around 46 per cent of the cases, followed by pelvic inflammatory disease in 14 per cent and uterine bleeding in 13 per cent, with a small number of other disorders, such as uterine prolapse, endometriosis, and so forth.

Only 4 of the 98 patients had undergone their subtotal operations at the clinic. The average age of the patients with cancer of the cervical stump was fifty-three years, with the majority in the forty to sixty-year range. The symptoms enumerated were the same as those of cancer of the cervix in general, with vaginal bleeding heading the list and leukorrhea the second most common complaint.

The treatment in the 84 true cases and in 14 coincident cases was surgical alone in 3 cases, radium and roentgen therapy in 81, radium treatment alone in 9, roentgen therapy alone in 3, and minor surgical procedures and irradiation in 2. The average lapse of time between subtotal hysterectomy and diagnosis of cancer in the retained cervix was 11.5 years. Leaving out the 3 cases in which surgical treatment alone was used, the rest were treated by irradiation, including the 2 which underwent minor surgical procedures as well as radiation therapy. Of the total of 82 true cases in which irradiation was used, 74 (90.2 per cent) were successfully traced, and all of the coincident cases were followed up. Of the total 95 patients treated by irradiation, 87 (91.6 per cent) were successfully followed up. The stage or extent of the lesions of the true cases is interesting (Table I): 40 were Stage I or II and 41 were Stage III or IV, 1 not being classified. In 50 (67.6 per cent) of the 74 traced true cases the patients survived for five years. The absolute survival rate was 61.0 per cent. In 13 coincident cases, only 13.7 per cent of the total group, 4 patients (30.8 per cent) had a five-year arrest of their cancer (Table II). Adenocarcinomas are believed to be more refractory to irradiation than squamous cell epitheliomas. There were 13 cases of the former (Table III), all true cases and all traced; 6 patients (46.2 per cent) survived five years.

TABLE I

FIVE-YEAR RESULTS OF RADIATION THERAPY SQUAMOUS CELL EPITHELIOMA AND ADENOCARCINOMA OF THE CERVICAL STUMP TRUE CASES

Stage	Patients		Surviving Five Years	
	Total	Traced	Number	Per Cent of Traced Patients
I	8	7	7	100
II	32	28	25	89.3
III	25	24	14	58.3
IV	16	14	4	28.6
Unknown	1	1	0	0
Total	82	74	50	67.6

The improvement in late results of treatment may have occurred in part from gradual changes in technique throughout the years. The main attack on the lesion has been by the use of radium placed in the stump of the cervix and intravaginally. The 50 mg. tube employed, filtered with 1 mm. of platinum, is only 4 mm. wide and the over-all length is only 19 mm., with the active length 11.7 mm. The method of treatment is an intensive broken-dose method, consisting of four applications into the cervical canal—two at the beginning of the canal and two at lesser dosage deep in the canal—and two or three vaginal treatments, employing a plastic cylinder usually of 1 cm. wall. Total dosage, treating the patients two or three times a week, averaged 4,000 to 4,700 mg.-hours, yielding around 4,500 gamma roentgens to point A and 1,150 gamma roentgens to point B. If the stump of the cervix had been partially removed by operation, precluding the use of radium deep in the canal, only two applications at the entrance of the canal were possible; then point A received only around 2,800 gamma roentgens and point B, 850 gamma roentgens. Thus, the main attack has been with intracavitary gamma radiation. Baud,[1] of the Curie Foundation, reported no cures with roentgen therapy or telecurietherapy alone. We have employed roentgen therapy concurrently or following the radium treatment to increase the roentgens at points A and B, and roentgen treatment has varied more than the radium application.

In the early review,[5] covering the years 1915 through 1930, moderate voltage, approximately 135 kv., was utilized up to 1923; from 1923 on, we used 200 kv. at 50 or 70 cm. distance, with half-value layer 0.98 mm. Cu, 540 r to each of four pelvic portals in four days. In Stage III and Stage IV lesions this latter dose was repeated in

TABLE II

FIVE-YEAR RESULTS OF RADIATION THERAPY SQUAMOUS CELL EPITHELIOMA AND ADENOCARCINOMA OF THE CERVICAL STUMP COINCIDENT CASES

Stage	Patients		Surviving Five Years	
	Total	Traced	Number	Per Cent of Traced Patients
I	2	2	1	
II	3	3	1	
III	3	3	2	
IV	4	4	0	
Unknown	1	1	0	
Total	13	13	4	30.8

TABLE III

FIVE-YEAR RESULTS OF RADIATION THERAPY ADENOCARCINOMA OF THE CERVICAL STUMP TRUE CASES

Stage	Patients		Surviving Five Years	
	Total	Traced	Number	Per Cent of Traced Patients
I	1	1	0	
II	5	5	4	
III	6	6	2	
IV	1	1	0	
Total	13	13	6	46.2

three months. This roentgen technique continued through the years of the present study, 1940 to 1949 inclusive. At the present time we are using 250 kv., 50 or 70 cm. distance, half-value layer 1.3 mm. Cu, and giving 1,800 to 2,400 r (air) to four pelvic ports in eighteen to twenty-four days.

Probably the greatly improved results of the present study are mainly due to a much more favorable group of patients. Decided improvement in gynecologic examinations prior to operation and improved surgical skill have resulted in a lesser number of incomplete operations for unsuspected malignant lesions, that is, fewer coincident cases. In the earlier group, 42.4 per cent of the patients treated represented coincident cases, in this study only 13.7 per cent. Also the cancers were less advanced; in the early study, 80 per cent of the true cases were Stage III or IV, as were 93 per cent of the coincident cases, compared to 50 per cent of the true cases and 54 per cent of the concident cases in the present study. These lesions in the present series were diagnosed much earlier than in the prior series.

SUMMARY

The present study concerns the results of radiation therapy in 95 cases of cancer of the cervical stump during the years 1940 through 1949. Eighty-seven (91.6 per cent) of the patients were traced. Of 74 traced patients with true cases of cancer of the cervix, 50 (67.6 per cent) survived five years. The absolute survival rate was 61.0 per cent. Of 13 coincident cases, all traced, 4 (30.8 per cent) survived five years. Of the total traced, 62 per cent survived five years; 57 per cent was the absolute survival rate.

These results are compared with results, reported in 1940 on 99 patients treated from 1915 through 1930. In this earlier study, five-year survivals were obtained in 26.3 per cent of the true cases and in 21.4 per cent of the coincident cases, or 24.2 per cent of the total traced.

Changes in technique have been minor. The marked improvement in results in the present study appears to be due to increased skill of gynecologists and of surgeons in detecting cancer of the cervix before subtotal hysterectomy is decided upon and also in earlier diagnosis of cancer of the cervical stump when it does appear. The percentages of coincident lesions and of Stage III or IV cancers diagnosed were much lower in the present than in the earlier study.

The results of treatment for cancer of the cervical stump in the present study compare favorably with our previously reported results of radiation therapy for cancer of the cervix in general.[6]

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A RADIUM APPLICATOR FOR USE IN THE TREATMENT OF CANCER OF THE UTERINE CERVIX*

By JAMES F. NOLAN, M.D., JOHN H. ANSON, M.S., *and* MAIDA STEWART, B.A.
LOS ANGELES, CALIFORNIA

THE purpose of this discussion is to present a radium applicator used in the treatment of cancer of the uterine cervix which has been designed, developed, and used with satisfactory results within the past five years.† The discussion has been motivated by a desire for such a presentation on the part of former Fellows in Radiation Therapy at the Los Angeles Tumor Institute and other therapists. This description will include the mechanical features of the apparatus, the technique of application, the dosimetry, and the clinical results associated with its use.

DESCRIPTION

The radium applicator consists of three integral parts, namely: the endocervical stem or tandem, the contracervical spacer, and the vaginal forniceal cylinders (Fig. 1). The apparatus is so designed that the endocervical portion with attached spacer can be introduced into the cervical canal in the axis of the vagina and then adjusted so that the tandem will assume an angle of 90° with the spacer. This permits the uterus to assume its normal anteflexed position with relation to the axis of the vaginal canal. The vaginal cylinders are attached to separate handles to allow for their introduction into the fornices separately. The cylinders are fitted into the concave portions of the central spacer, and their handles are themselves concave to integrate with the convex surfaces of the central handle. When placed in position, a ring slips over the three portions of the handle to fix them. The angle of the handle in relation to the spacer is 30°, which approaches the normal axis of the vagina. The extremity of the central portion of the handle protrudes from the vagina, and has a metal loop through which the straps of a cross-binder may be passed in order to fix the whole apparatus in relation to the pelvis.

The applicator is of chrome-plated brass, and the various portions of it may be sterilized by boiling. All portions of it may be separated for loading and cleaning. The tandem is manipulated by the knurled knob at the protruding end of the handle. It is in sectional lengths of 28, 50, and 72 mm. with inside diameter of 4 mm. and outside diameter of 7 mm. The wall thickness is 1.5 mm. The spacer measures 5 mm. at the thin section of the concavity sep-

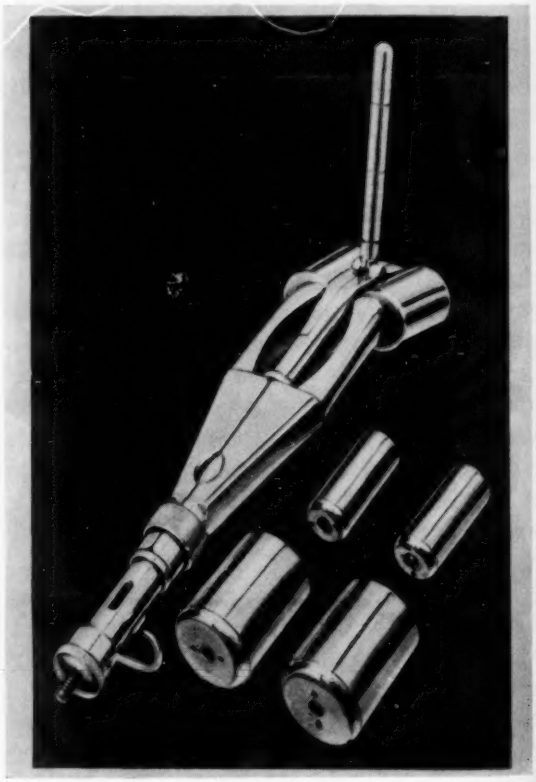


FIG. 1

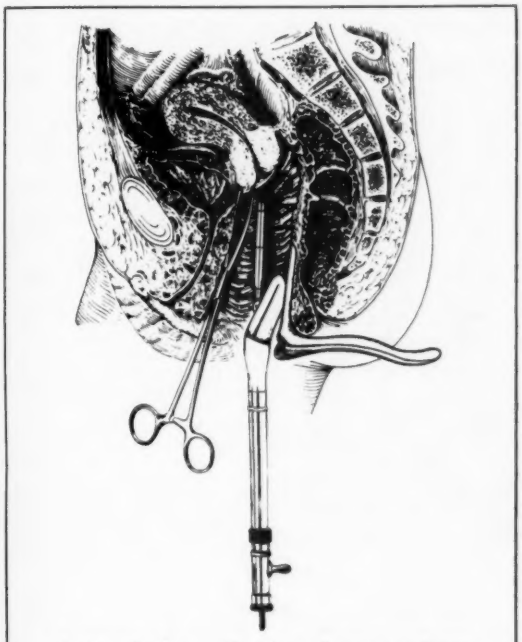
* From the Los Angeles Tumor Institute.

† Miss Lucille DuSault, who is now physicist at the Henry Ford Hospital in Detroit, Michigan, was highly instrumental in preparing the early designs and in the development of the prototypes of this apparatus. We gratefully acknowledge her able participation.

arating the ovoids. The handle is 19 cm. long. The cylinders contain 4 mm. of lead in the ends in order to decrease the radiation toward the bladder and the rectum. The inner medial quadrants of the cylinders are lead to block cross-radiation toward the rectum. They are 1.5, 2.0 and 2.5 cm. in diameter and are interchangeable on their handles to allow for variations in the geography of the vaginal fornices.

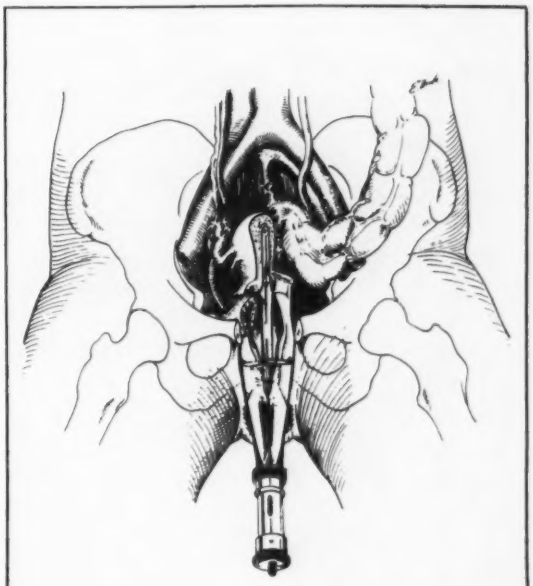
APPLICATION

In terms of clinical application the fact that the tandem may be depressed upon the spacer allows for ease of introduction into the cervical canal under good vision. It then can be raised to the normal position before the vaginal cylinders are introduced, allowing for the utilization of the available space in the fornices without anatomic distortion. Manipulation of the apparatus in separate units, each with its own handle, affords some protection to the hands of the operator. Once the apparatus is integrated, one can be certain that each radium source will remain in an exact relationship with the others. After the rectum has been packed, the fixation of the protruding handle to the abdominal cross-binder gives further assurance that the apparatus will remain in place. The firm pressure of the binder keeps the vaginal portion in direct apposition with the vaginal walls, but this pressure need not be so great as to cause the patient discomfort. The extra weight of the apparatus due to the lead inserts in the cylinders is not too discomforting because of the support afforded by the binder. With the intense radium loading which has been used, exposure times have seldom exceeded thirty hours and this is repeated after a two-week interval. During this time most patients do not complain of discomfort. The application is illustrated in Figures 2, 3 and 4.



Lateral view. Tandem depressed on spacer for introduction into cervix

Fig. 2.

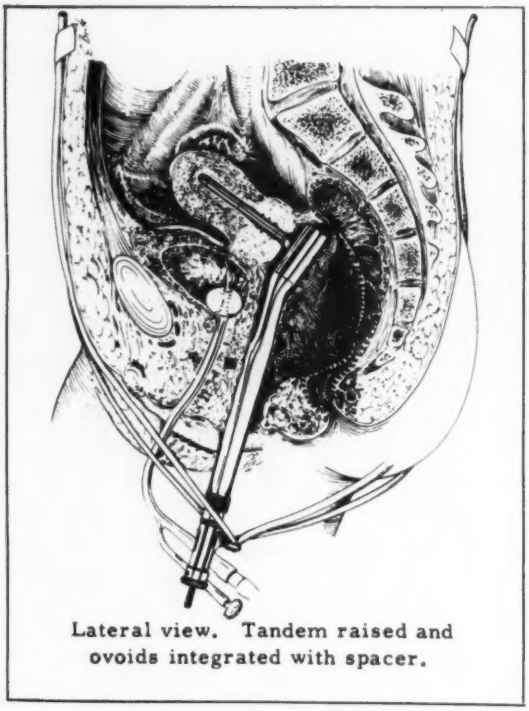


Anterior-posterior view. Tandem, spacer and ovoids in position.

Fig. 3.

PHYSICAL MEASUREMENTS

The radiation pattern surrounding this applicator was studied by means of film dosimetry.[4] Each combination of tandem



Lateral view. Tandem raised and ovoids integrated with spacer.

FIG. 4.

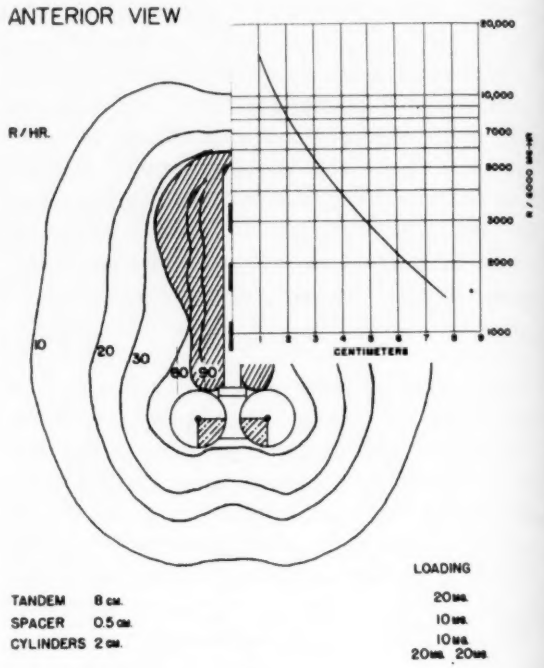


FIG. 5.

and vaginal cylinder was reproduced in a pressdwood phantom and isodoses were constructed. The applicator has been designed for standard 10 mg., 0.5 Pt filter, 1.5 cm. active length sources. The usual loading has been with unit sources in the cervical and mid-portions of the tandem and twice unit sources in the distal end of the tandem and in the cylinders. The resultant isodoses from such a loading are shown in Figures 5 and 6 in terms of r/hr. The most intense area of radiation lies in what would be the fundus of the uterus, but there is good uniformity of dosage in the region of the cervix, fornices, and proximal parametria. The decrease in radiation directed toward the rectum and bladder because of the lead inserts in the cylinders can be seen. In the diagrams the radiation along the A-B axis at the level of the internal os is also shown in terms of an exposure of 6,000 mg. hr. with this loading. This is the usual exposure which has been utilized and the "lateral-throw" from the applicator yields theoretically effective amounts of radiation at a distance of 4 centimeters. The area which may receive theoretically necrosing doses is well within 1 cm.

Studies were also made to ascertain the

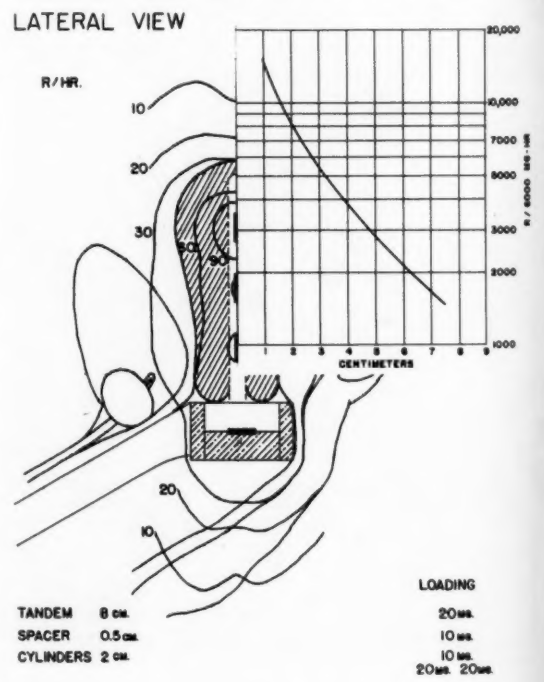


FIG. 6.

difference in dose level along the axis of the internal os, with variation in the number of sources in the tandem while maintaining the same set of cylinders, and with variation in the size of the cylinders maintaining the same tandem. These curves are reproduced in Figure 7. One can see that the longest tandem gives the best dosage distribution, as does the largest cylinder. However, the difference between the 2.5 cm. and the 2.0 cm. diameter cylinder is very slight. Since the largest cylinder seldom can be used because of constriction and distortion of the fornices the slight advantage of this size is not practical. However, it does seem advantageous to use the longest tandem possible.

Another comparison was made among the radiation distribution curves along the A-B axis derived from the Ernst and Manchester applicators,[1,3] which are similar in concept to the present one. These curves are also shown in Figure 7 in terms of r/mg. hr., and normalized at 1,500 r at 1 cm. There are only slight differences among them, but on a basis of uniformity as described by the A/B dose ratio there is a slight superiority in favor of the present applicator.

CLINICAL RESULTS

Between the years 1952 and 1956 this applicator or its prototypes has been used some 253 times in 134 patients. In 109 patients this was the sole method of radium application in the primary treatment scheme.

Table 1 lists the number of patients so treated according to stage of disease with the average mg.-hr. exposure, and the average total radium plus external cobalt 60 radiation doses at Points A and B, as well as the average over-all treatment times. The applicator was used mainly in patients with early lesions, with the radium exposure decreased with advancement of disease. The total doses at A increased in Stage III, and the total doses at B increased in Stage IV, because the supplemental external radiation was necessarily increased in these advanced stages at the expense of the doses contributed by local radium implantation.[2] The relative number of patients treated with this applicator are fewer with advanced stages of the disease; in these cases other means of radium implantation (such as simple tandems, interstitial needles or intravaginal bombs) were utilized because of destruction or distortion of the natural geog-

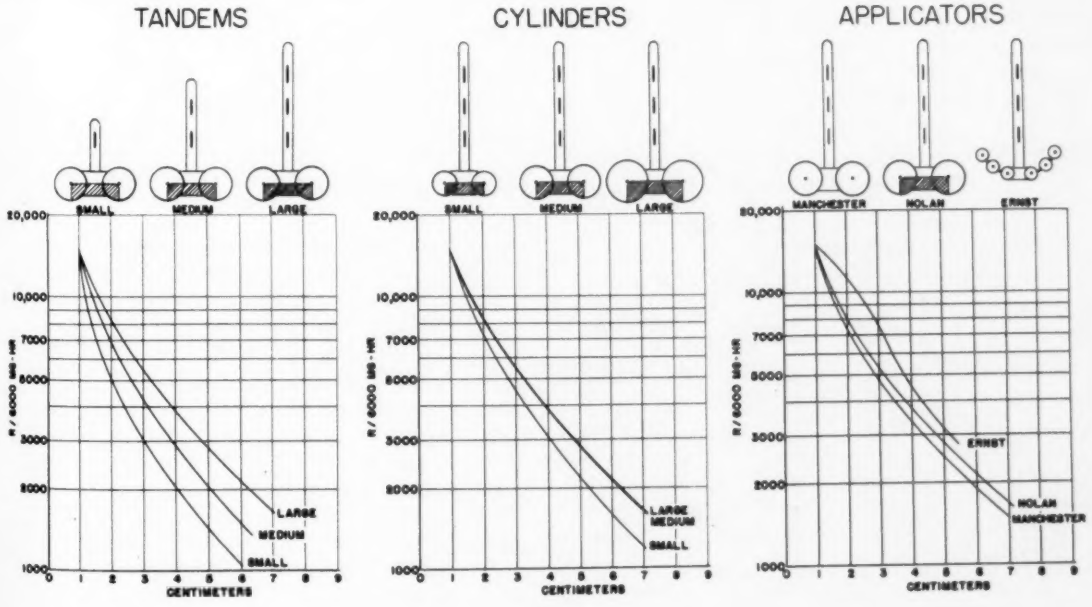


Fig. 7.

TABLE I

CARCINOMA OF CERVIX
Los Angeles Tumor Institute
1952–1956
Tandem-Cylinder Applicator Used Exclusively for Radium Application
RELATIONSHIP OF AVERAGE DOSAGE TO STAGE OF DISEASE

Stage	Number of Cases	Radium Exposure	Total Dose Ra plus Ext. Radiation		Total Time in Days
			at A	at B	
		mg.-hr.	r	r	
O	5	4675	6060	2434	34
I	54	5334	6710	3585	43
II	37	5156	6973	3762	48
III	11	4485	7330	4180	53
IV	2	3195	6102	4208	54

raphy of the vagina. A few Stage 0 patients were treated by radiation in preference to surgery because of clinical reasons.

The reactions and complications to treatment are shown in Table II. These were judged in terms of severity, and all patients complaining of such reactions were included. There were 2 patients who developed severe reactions; in both this was proctitis, and one was subjected to a colostomy. The others were controlled by conservative measures. The most common reaction was local pressure areas in the lateral vaginal vault due to the use of cylinders which were too large. This has been seen infrequently in recent months, since care has been taken to avoid it. Only on 3 occasions was there any local sloughing of consequence, and in 2 of these cases there had been preliminary cauterization of the cervix before therapy had been started.

The results of these treatments in terms of the present status of the patients is shown in Table III. Although they appear favorable, the time at risk for this group is necessarily short and the series includes favorable cases in the main.

TABLE II

CARCINOMA OF CERVIX
Los Angeles Tumor Institute
1952–1956
Tandem-Cylinder Applicator Used Exclusively for Radium Application
LOCAL COMPLICATIONS AND REACTIONS TO TREATMENT

Stage	Local Necrosis			Cystitis			Proctitis		
	Mild	Mod.	Severe	Mild	Mod.	Severe	Mild	Mod.	Severe
O	1	—	—	—	1	—	—	—	—
I	6	—	—	4	2	—	—	2	1
II	6	2	—	—	—	—	—	1	—
III	—	1	—	—	—	—	—	—	1
IV	—	—	—	—	—	—	—	—	—

DISCUSSION AND SUMMARY

The applicator that has been presented is far from unique, and can be described only as a modified apparatus. The modifications have been directed by the natural limitations imposed upon its design by the physical characteristics of radium itself as well as the anatomic relationships of the uterine cervix and the physiologic characteristics of cervical tumors. In its evolu-

TABLE III

CARCINOMA OF CERVIX
Los Angeles Tumor Institute
1952–1956
Tandem-Cylinder Applicator Used Exclusively for Radium Application
RESULTS IN TERMS OF PRESENT STATUS OF PATIENTS

Stage	Number of Cases	Alive with Disease	Dead with Disease	Alive without Disease	
O	5	0	0	5	100%
I	54	1	3	50	93%
II	37	5	3	29	79%
III	11	1	4	6	55%
IV	2	1	1	0	0%
Total	109	8	11	90	83%

tion, compromises have had to be made in order to arrive at a final design which is simple, stable, and economic in construction. Thus, it is far from a perfect or universal applicator.

Of course, there are many techniques of radium application presently in use throughout the world, and each of these has its features of advantage and disadvantage. There can be no attempt made here to describe all of these in detail other than to say that they vary from interstitial needle implantation, which can be the most individualized of radium treatments, to the Neary applicator, which yields the most advantageous type of dosage pattern.[1] Any fixed tandem-vaginal source type of apparatus sacrifices flexibility and loses a desirable characteristic in adaptability to each individual lesion. Any individual multiple-source type of applicator sacrifices stability and reproducibility to a certain extent. It seems logical to assume that all lesions cannot be treated best by one type of radium technique.

Thus, we cannot express any superiority for the apparatus in question over all other methods of treatment. We can merely state that, thus far, it has been a very satisfactory addition to our armamentarium. It has been used more and more in preference to other methods of radium application because of the high percentage of early lesions seen in our practice; because of the addition of megavoltage external radiation which frequently makes more complicated radium implantations less necessary; and because it offers some protection to the operator from excessive radiation exposure to his hands.

The worth of any apparatus can be judged only by its clinical usefulness to any individual operator within his own experience. However, it is thought that the description of this apparatus which has been judged satisfactory in our experience may be of interest to others.

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A GRAPHIC METHOD OF RECONSTRUCTING RADIUM NEEDLE IMPLANTS FOR CALCULATION PURPOSES*

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LAKEWOOD, COLORADO

IN CALCULATING the tissue dose from interstitial radium needle implants in which there are multiple parallel or angled planes, or in which a row of needles is curved, it is of great importance to obtain an exact measurement of the separation between the planes, the angulation, or the curvature. Frequently this is quite difficult, and compromises are made in exactitude for the benefit of facility in calculation. The difficulty can sometimes be resolved by studying the preliminary roentgenograms and having others made in which the implant is seen "end-on." This can be done in only a small percentage of cases (a submento-vertical view of a tongue implant, for instance), and frequently is quite time consuming, requiring multiple roentgenograms before a satisfactory one is obtained. It is the purpose here to present a general method of obtaining this "end-on" view by geometrical projection and transposition of coordinates with a special simplified application which can be used in the majority of cases. The method requires only the standard right angle roentgenograms and is neither time consuming nor difficult, but is accomplished methodically and accurately to give a graph of this "end-on" view from which measurements can be directly taken.

GRAPHIC PROJECTION

The location of an object in space is determined by its relation to any three dimensional reference system and is represented by its projection on the three right angle planes defined by the axes of such a reference system. If the projection of the object on two of the three planes is known, its relation to all three axes is defined and the projection on the third plane may be constructed.

Figure 1*A* shows two radium needles in space with their two standard right angle roentgenograms. The $x-z$ plane represents the anteroposterior film and the $y-z$ plane represents the lateral film. The common side of the film represents the z axis. The ends of the anteroposterior and lateral films represent the x and y axes respectively. These axes determine the plane upon which the needles are to be projected. This projection will appear the same and remain an accurate representation of the position of the needles no matter were the $x-y$ plane is positioned along the z axis, provided it remained perpendicular to the z axis. Therefore, any two lines (hereafter called "baselines") drawn on the films, which are perpendicular to the common side, may be used to construct the desired projection. Points on the films representing the ends or centers of the needles are projected prependicularly onto the baselines, and distances from the common edge to the projected points, after correction for magnification, are plotted on graph paper to obtain the $x-y$ projection. If an arbitrary zero point on the baseline is used for measuring rather than the common edge of the films, the resultant projection will merely be located differently on the graph without changing the relationship of the needles to one another.

If, as in Figure 1*A*, the needles on the $x-z$ and $y-z$ planes are parallel to the z axis, they will always appear on the result-

* This project was done under an American Cancer Society fellowship in Radiotherapy at M. D. Anderson Hospital and Tumor Institute, Houston, Texas.
† Currently at St. Anthony Hospital, Denver, Colorado.

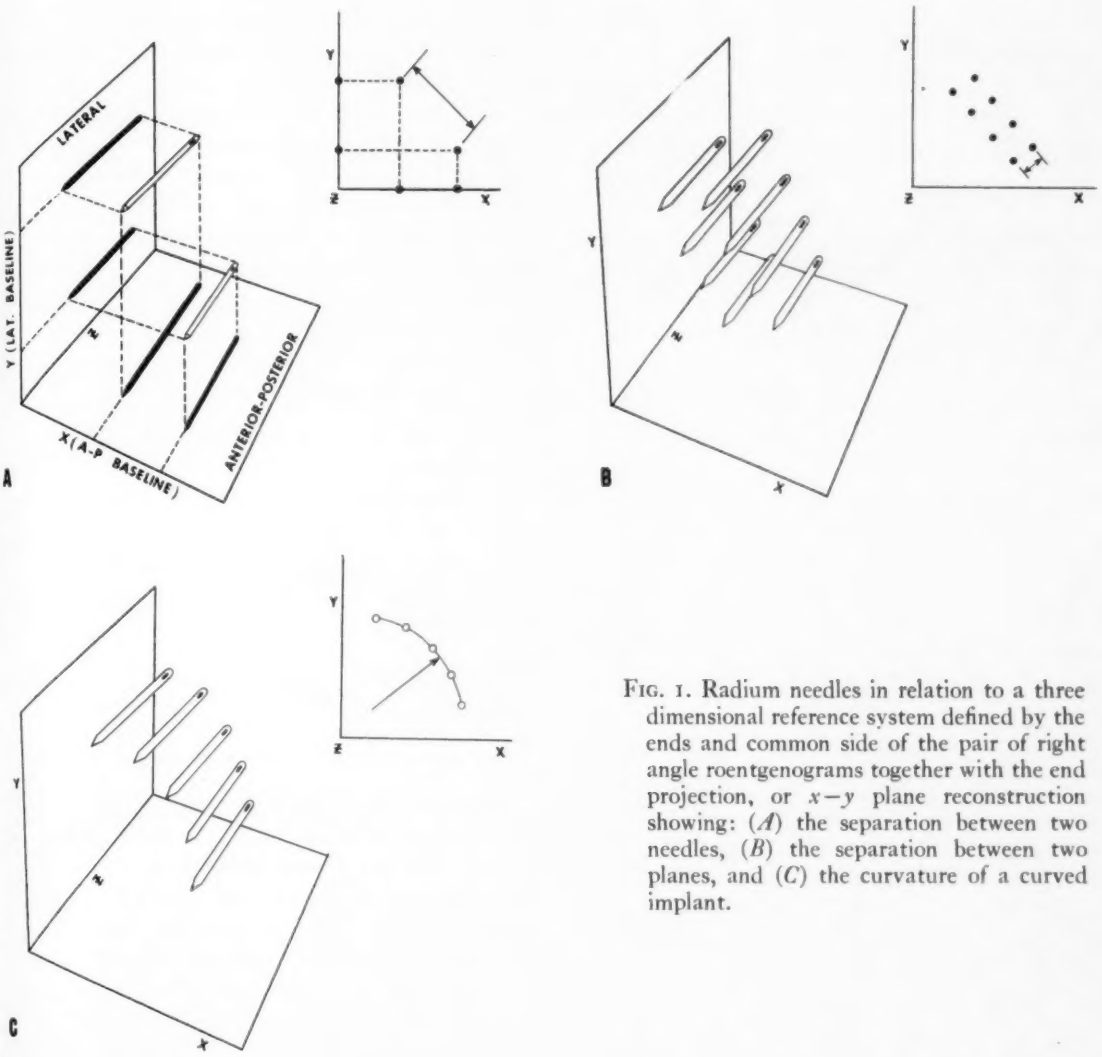


FIG. 1. Radium needles in relation to a three dimensional reference system defined by the ends and common side of the pair of right angle roentgenograms together with the end projection, or $x-y$ plane reconstruction showing: (*A*) the separation between two needles, (*B*) the separation between two planes, and (*C*) the curvature of a curved implant.

ant graph as points. Since this is a non-distorted end-on projection, therefore the separation between these needles can be accurately measured on the graph. If there are two or more planes (Fig. 1*B*), the separation between these planes can be measured. If the implant is curved (Fig. 1*C*), the actual curvature can be seen and measured.

In the foregoing examples, the desired axis of projection for obtaining the end-on view has been along the axis of the needles. In the case of an angled implant (Fig. 2), however, the line of intersection of the planes is taken as the axis of projection and separate points must be projected for each end of a needle, being connected on the graph to show the full length of the needle. Therefore, on the graph we can measure not only the angulation, but also the total width of the implant.

In this type of implant many of the needles will be superimposed on the graph and it may be more expedient to select representative needles for projection rather than to go through a process of projecting all the needles. The selection of the representative needles can be quite accurate if stereoscopic films are obtained, but if these are not available, it will be more accurate in even slightly irregular implants to project several needles on the graph and

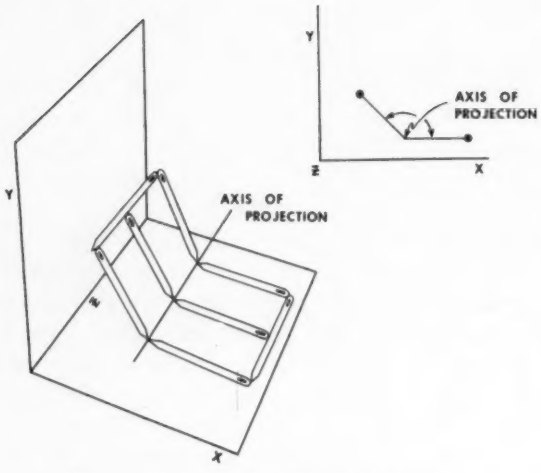


FIG. 2. An angled implant together with its end projection.

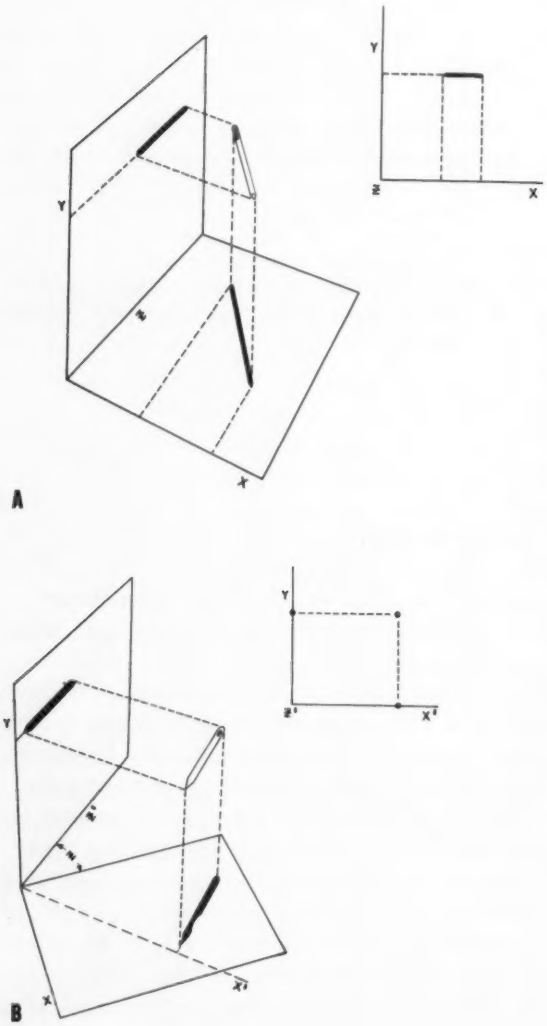


FIG. 3. (*A*) A radium needle situated in a reference system in which the $x-y$ plane is not a true "end-on" projection. (*B*) A view of films showing rotation of the anteroposterior film, and the setting up of the x^1, y, z^1 reference system, together with the graph of the x^1-y plane which is a true "end-on" projection.

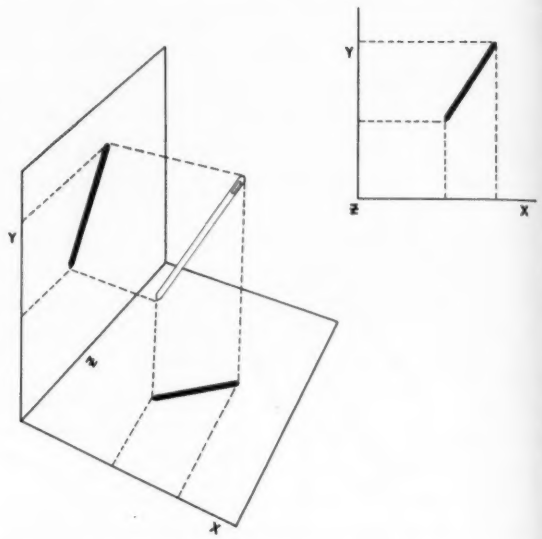


FIG. 4. A radium needle positioned so that it is parallel to neither of the defining planes, with its $x-y$ projection.

take the average projection for calculation purposes.

TRANSPOSITION OF COORDINATES

The above procedure is applicable only when the desired axis of projection is parallel to the z axis (the common edge of the films), otherwise the radium system must actually or theoretically be rotated in space to meet this condition before such a projection can be made. It is often impossible to obtain roentgenograms with the implant in the correct position for projection and so the rotation must be theoretical. This can be done by transposing the coordinates of one three dimensional reference system to those of another in which the desired axis of projection for an "end-on" graph is parallel to the z axis.

If an object is rotated in space about one axis of a three dimensional reference system, all points maintain their relation to

the axis of rotation, but change with relation to the other two axes. The image on the plane defined by the other two axes does not change except in location on the plane. Thus, if an object is rotated on the roentgenographic table about an axis perpendicular to the table, all points maintain the same height above the table, but will appear in a different position on the film while maintaining the same appearance. The same effect is obtained by rotation of the original roentgenogram. Thus, if in the right angle films of a radium implant the desired axis of projection is perpendicular to the baseline on the lateral film (the y axis), the anteroposterior film may be rotated so that the desired axis of projection is parallel to the z axis, as represented by the common side of the lateral film.

Since the original x, y, z reference system is, by definition, the common side and ends of the films, this rotation, in effect, sets up a new reference system defined by the y, x^1, and z^1 axis, in which the z^1 axis is parallel to the desired axis of projection. A new baseline corresponding to the x^1 axis is drawn perpendicular to the z^1 axis and a

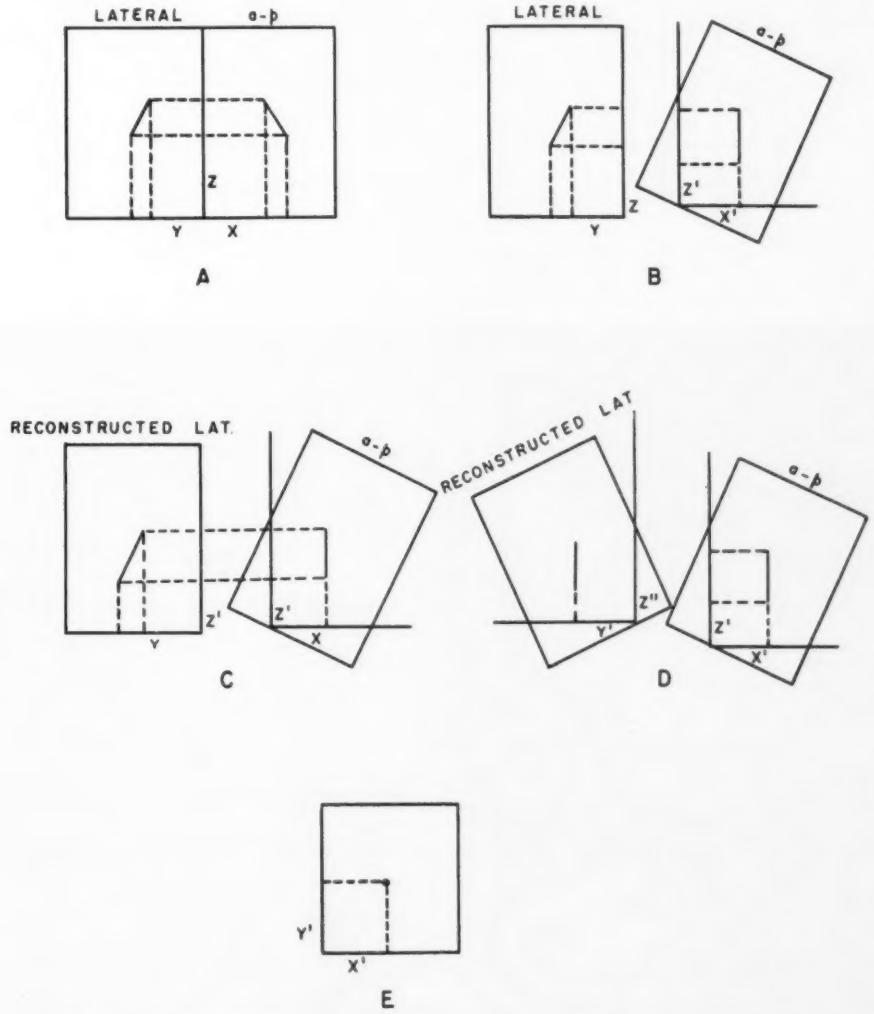


FIG. 5. The steps in obtaining a true end-on projection using the double rotation technique. (*A*) The nonrotated films; (*B*) rotation of the anteroposterior film; (*C*) reconstruction of the lateral projection; (*D*) rotation of the reconstructed lateral projection; (*E*) final "end-on" graph of the x^1-y^1 projection.

graph of the x^1-y plane will be the desired end-on projection. Figure 3*A* shows a radium needle in space which fits the above situation together with its graph of the $x-y$ plane, which is not a true end-on projection. In Figure 3*B*, the anteroposterior film has been rotated, a new baseline (x^1) drawn, and the resultant graph of x^1y is a true end-on projection.

This simple act of drawing the baseline perpendicular to the desired axis of projection in one of the pair of right angle roentgenograms enables an end-on graph to be constructed in the majority of interstitial needle implants.

Instances do arise, however, in which it is impossible to obtain a pair of right angle roentgenograms in which the desired axis of projection is perpendicular to the original baseline in either of the films. In this case, a double rotation must be performed, but this cannot be done without an inter-

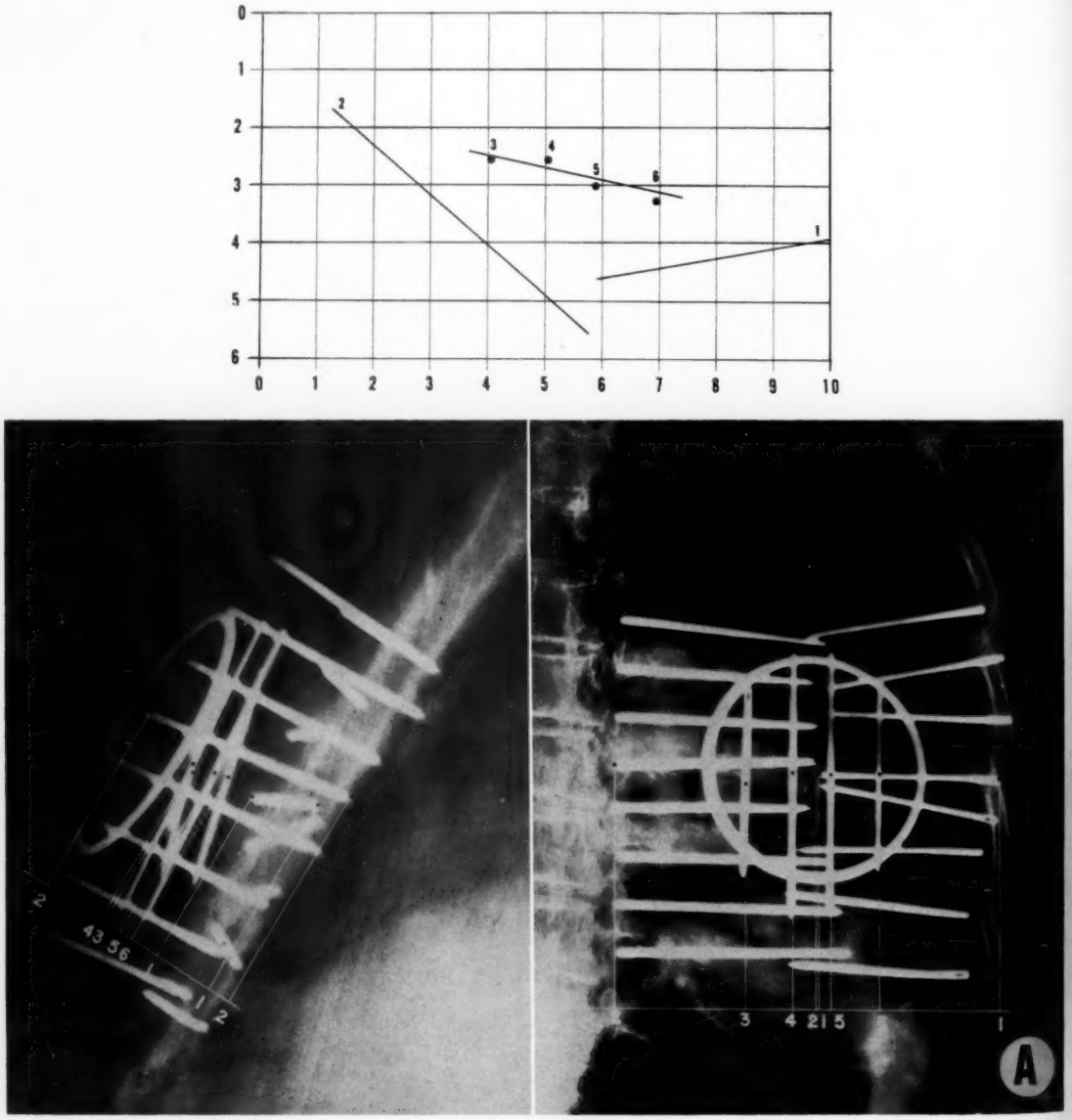
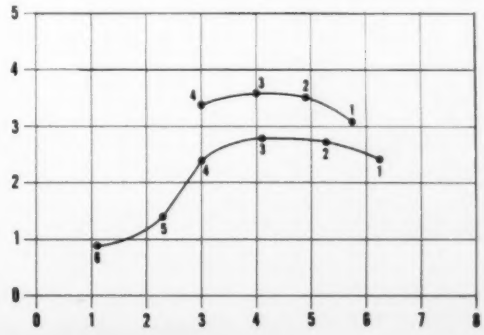


FIG. 6. (*A*) The right angle films of a three plane implant together with the "end-on" projection obtained by the single rotation technique.

mediate step. The first rotation is performed as before, but the lateral film is then no longer a valid image of the projection of the needles with reference to the x^1, y, z^1 system since its defining points are relative to the original z and y axes. Therefore, a new lateral projection must be constructed utilizing the z^1 and y axes. This $y-z^1$ graph, or reconstructed lateral projection, can now be rotated (in effect rotating the needles around the x^1 axis in space and setting up a new reference system defined by x^1, y^1, z^2), and a new baseline, y^1, drawn. The graph x^1y^1 will now present a true end projection of the object.

Figure 4 represents a radium needle in space which is parallel to the z axis in neither of the films together with its graph which is not a true end-on projection. Figure 5 shows the steps involved in obtaining the true end-on projection. Of the original roentgenograms (*A*), the anteroposterior is rotated, new baseline drawn, and the new x^1 and z^1 axes defined (*B*). Using points projected on the z^1 and the original y axes, a graph of the reconstructed lateral projection is made (*C*). This reconstructed lateral is rotated, a new baseline drawn, and the axes y^1 and z^2 defined (*D*). The final graph, x^1, y^1, is constructed (*E*), giving a true end-on projection.

Figures 6*A* and 6*B* are examples of actual cases in which this method has been used.



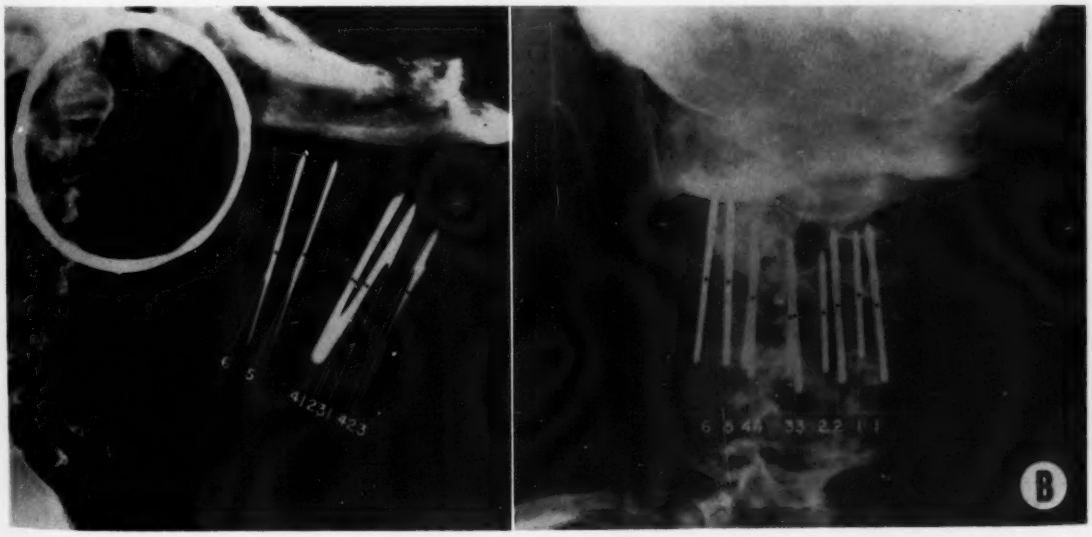


Fig. 6. (*B*) The right angle films of a double curved implant together with the end-on projection obtained by the single rotation technique. The baselines are drawn and perpendiculars dropped from the needle ends or centers. Distances along the baselines from an arbitrary zero point to the perpendiculars are measured, corrected for magnification and plotted to give the "end-on" projection.

SUMMARY OF THE METHOD

A. Desired axis of projection perpendicular to the end of at least one of the pair of roentgenograms.
   1. Locate the axis of projection on both films.
   2. Draw baselines perpendicular to axes of projection.
   3. With lines perpendicular to the baseline, project the ends of other identifiable points of the needles onto the baseline.
   4. On the baselines, measure the distances of the projected points from an arbitrary zero point.
   5. Correct each distance for magnification.
   6. On the perpendicular axes of the centimeter graph paper, lay out the true distances of the points, (the points from the anteroposterior roentgenogram on the horizontal axis and those from the lateral roentgenogram on the vertical axis), and plot points.
   7. Take measurements of separation, curvature, angulation, and width of implant for use with Paterson-Parker tables.

B. Desired axis of projection not perpendicular to the end of either film.
   1. On lateral film draw baseline "y" parallel to the end of the film.
   2. Project points as in steps A (3)–(5).
   3. On anteroposterior roentgenogram, locate desired axis of projection.
   4. Draw baseline x^1 perpendicular to axis of projection and locate points as in A (3)–(5).
   5. Draw baseline z^1 perpendicular to baseline x^1 (parallel to desired axis of projection) and locate points as in steps A (3)–(5).
   6. Using corresponding points from the y and z^1 axes, construct graph of revised lateral projection as in step A (6).
   7. On graph of revised lateral film, locate desired axis of projection, draw perpendicular baseline y^1, project points, and measure distances.
   8. From points on baselines x^1 and y^1, construct graph of true end projection as in step A (6).
   9. Take measurements.

SUMMARY

A method is presented for constructing a graph to give an end-on projection of an interstitial implant from which measurements can be directly taken, giving the curvature, angulation, and size of an implant or the separation between the planes of a multiple plane implant.

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I wish to express my thanks to Gilbert H. Fletcher, M.D., Robert J. Shalek, Ph.D., William H. Storey, M.A., and to the others of the M. D. Anderson Hospital who have aided in the preparation of this manuscript.

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THE USE OF INTERSTITIAL RADIUM DOSE RATE TABLES FOR OTHER RADIOACTIVE ISOTOPES*

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MANY different radioactive isotopes are currently used in interstitial radiation therapy. In estimating exposure dose from such isotopes, it is convenient to use the standard radium exposure dose rate tables. This can be done approximately by multiplying the tables by the ratio of the specific gamma-ray emission of the isotope to that of radium. This procedure, however, neglects differences in absorption and scatter. The purpose of this paper is to determine the magnitude of the correction factor which should be applied to the radium tables when they are used for other isotopes. It will be shown that for points within about 5 cm. of the source of radiation the correction factor is less than 10 per cent when the gamma ray energy is between 0.25 and 2 mev.

METHOD

The exposure dose rate in air at a point $\mathcal{Q}$ (Fig. 1A) from a point source of radiation at P will, for practical purposes, depend only on the inverse square law. If the specific gamma-ray emission (roentgens per millicurie-hour at 1 cm.) of the isotope is given the symbol Γ, then the exposure dose rate in air, D_{air}, at a distance d cm. from the point source is

$$D_{air} = \Gamma/d^2 \text{ r/mc-hr.} \qquad (1)$$

When the isotope is an infinitely large water phantom, two factors will modify the dose rate at $\mathcal{Q}$ from what it was in air. The first factor is the absorption of some gamma rays in the water between P and $\mathcal{Q}$ (γ_2, Fig. 1B). This factor will tend to decrease the exposure dose rate measured at $\mathcal{Q}$. Let us call the absorption factor A. The second factor is the scattering of some of the gamma rays (γ_3, Fig. 1B) so that they enter the volume of interest, produce ionization, and increase the measured dose rate. We can call this exposure dose rate build-up factor B. The absorption factor, A, and the build-up factor, B, depend on both the energy of the gamma rays and the distance, d, between the point source of radiation and the point of interest. Accordingly, the mathematical relation is:

$$D_{water} = D_{air}AB \text{ r/mc-hr.} \qquad (2)$$

Thus the product of A and B is the water–air dose ratio and is, therefore, the correction factor which should be applied to the dose rate in air when it is desired to obtain the dose rate of the same relative point in water.

The widely used radium dose rate tables are actually tables of exposure dose rate in air, since absorption and scatter were neglected when they were computed.[7] The tables can, therefore, be used with any isotope if they are first multiplied by the ratio of the specific gamma-ray emission of the isotope to radium and then multiplied by the correction factor AB. To summarize, the ratio of the exposure dose rate of another isotope, I, to radium is, using equation 1,

$$\frac{D_{air_I}}{D_{air_{Ra}}} = \frac{\Gamma_I}{\Gamma_{Ra}} \qquad (3)$$

Therefore,

$$D_{air_I} = \frac{\Gamma_I}{\Gamma_{Ra}} D_{air_{Ra}}. \qquad (4)$$

* From the Radiology Department of the Hospital of the University of Pennsylvania. This investigation was supported in part by a research grant (1984) from the National Cancer Institute, Public Health Service.
Presented at the Thirty-ninth Annual Meeting of the American Radium Society, Quebec City, Quebec, Canada, May 29–June 1, 1957.

Substituting this expression in equation 2,

$$D_{\text{water}_I} = \frac{\Gamma_I}{\Gamma_{Ra}} D_{\text{air}_{Ra}} AB. \qquad (5)$$

In practice, if the decay scheme is known, the specific gamma-ray emission for the isotope, Γ_I, can be calculated, or if the radioactivity of the source can be determined independently, Γ_I can be measured. Γ_{Ra} is the accepted value for the gamma-ray emission from a point source of radium, 8.4 r/mg.-hr. at 1 cm. with 0.5 mm. Pt filtration. $D_{\text{air}_{Ra}}$ is obtained from the appropriate radium dose rate table. The correction factor AB as a function of gamma-ray energy and distance will be calculated in this paper.

The absorption and build-up factors have been studied previously by others. This paper applies data available in the literature to the specific problem of interstitial dosimetry. The absorption factor A can be determined by the general exponential absorption equation. The absorption coefficient data of White[10] were used for this calculation. The build-up factor, B, for a point source in an infinite medium has been studied by Goldstein and Wilkins[3] for energies above 0.255 mev., in connection with shielding problems.* Their results in water are applicable also to the problem considered here. As an example of the data, the variation of the absorption and build-up factors as a function of distance is shown for a typical gamma-ray energy of 0.5 mev. in Figure 2.

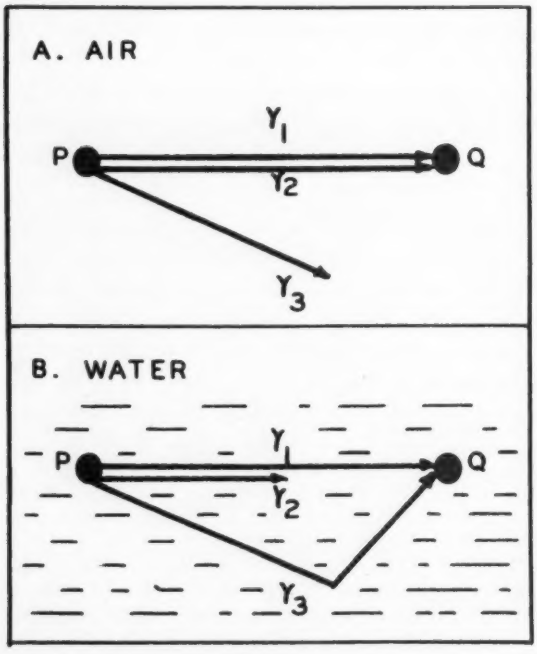

FIG. 1. Comparison of the exposure dose rate at Q from a source of gamma rays at P. In air (A) the dose rate at Q is principally governed by the inverse square law. In water (B) the effect of absorption (γ_2) in dose decrease and of scatter (γ_3) in dose build-up must also be taken into consideration.

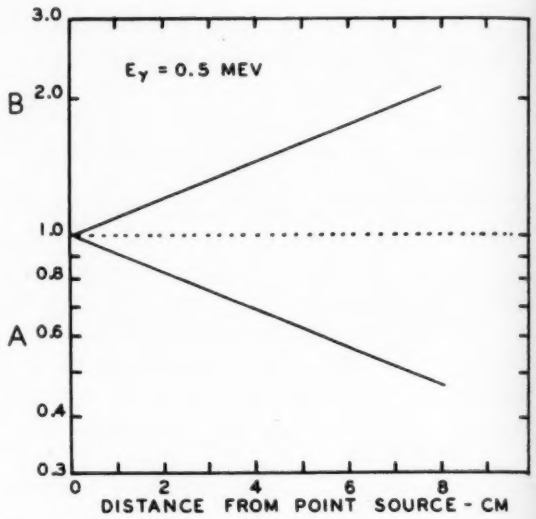

FIG. 2. The variation of the absorption factor, A, and the build-up factor, B, as a function of distance from the source for gamma rays of 0.5 mev. initial energy.

The results of the calculation of the water-air dose rate ratio, which by equation 2 is the same as the correction factor AB, are presented in Table 1 and Figure 3 as a function of gamma-ray energy and distance from the point source to the point of interest.

DISCUSSION

Calculations based on two independent sets of published data confirm the expectation that the effects of the absorption fac-

* It was found that the data of Goldstein and Wilkins[3] for a point source in water in the region of clinical interest ($0 < \mu d > 1$; $0.255 < E > 2$ mev.) are represented to an accuracy of about 2 per cent by the empirical equation

$$B = \exp\left[(0.77/E^{0.29})\mu d\right].$$

Table I

CALCULATION OF WATER–AIR DOSE RATE RATIO

E mev.	μ water cm.$^{-1}$	d cm.	A	B	$D_{water}/D_{air}=AB$
0.255	0.125	0.5	0.939	1.077	1.011
		1.0	0.882	1.158	1.021
		2.0	0.779	1.332	1.036
		5.0	0.535	2.040	1.091
		8.0	0.367	3.140	1.150
0.500	0.096	0.5	0.953	1.046	0.997
		1.0	0.908	1.095	0.994
		2.0	0.825	1.198	0.988
		5.0	0.619	1.574	0.974
		8.0	0.465	2.061	0.958
1.000	0.071	0.5	0.965	1.029	0.993
		1.0	0.931	1.056	0.983
		2.0	0.868	1.116	0.969
		5.0	0.700	1.314	0.920
		8.0	0.567	1.550	0.879
2.000	0.049	0.5	0.976	1.012	0.992
		1.0	0.952	1.031	0.982
		2.0	0.908	1.062	0.964
		5.0	0.783	1.167	0.914
		8.0	0.675	1.280	0.865

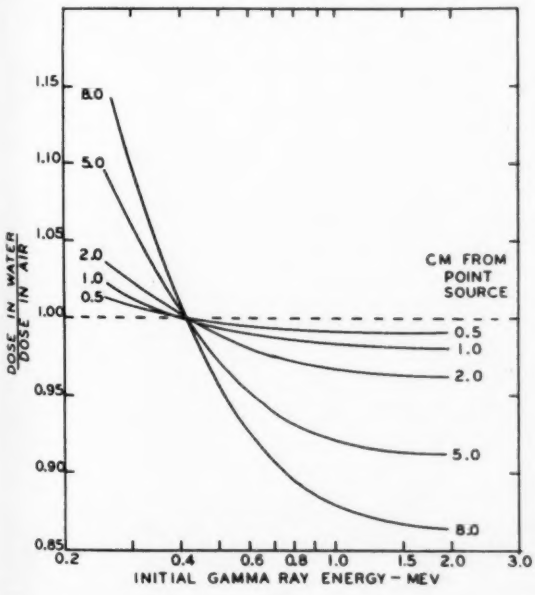

Fig. 3. Water–air dose rate ratio as a function of initial gamma-ray energy for various distances from a point source of gamma rays, showing that the correction factor for gamma rays of initial energy between 0.25 and 2 mev. is less than 10 per cent for points within 5 cm. of the source.

tor and the build-up factor very nearly cancel each other over a wide range of distance and of gamma-ray energy. This is surprising since each factor may differ from 1 by as much as a factor of 2. From Figure 3 it is seen that the correction factor for points within 5 cm. of the source, which includes almost all points of clinical interest in interstitial therapy, is less than 10 per cent for gamma-ray energies between 0.25 and 2 mev. Since isotopes that are useful for interstitial therapy have average gamma ray energies within this range, the widely adopted procedure of neglecting the correction factor AB in equation 5 is justified if ± 10 per cent limits of the accuracy of the dose rate estimation are accepted. This approximation seems to be reasonable because the error introduced by the uncertainty in reconstructing the geometric distribution of the sources of radiation is likely to be considerably larger than 10 per cent.

For a gamma-ray emitting isotope with an energy of about 0.4 mev. it is seen that the absorption and build-up factors just balance each other.* For lower energies, the build-up factor predominates and the dose rate in water is higher than in air; for higher energies, the absorption factor is larger and the dose rate in water is lower. It should be emphasized that these results apply only for distances from the point source that are less than about 10 cm. For great distances the absorption factor always predominates.

It can also be shown that the correction factor approaches 1 as the distance from the point source approaches zero. In Figure 2 it is seen that both A and B uniformly approach 1 as the distance approaches zero. Therefore, the product, which is the correction factor AB, must also uniformly approach 1 as the distance from the point source approaches O. It should be pointed out that these calculations apply strictly to point sources only. Differences in dose

* This statement can be demonstrated mathematically by the use of the exponential absorption formula and the empirical build-up factor equation. Equation 2 can be written as

$$D_{water}/D_{air}=AB=\exp(-\mu d)\exp[(0.77/E^{0.29})\mu d].$$

If D_{water}/D_{air} is set equal to 1, the value of E that satisfies the equation is 0.4 mev.

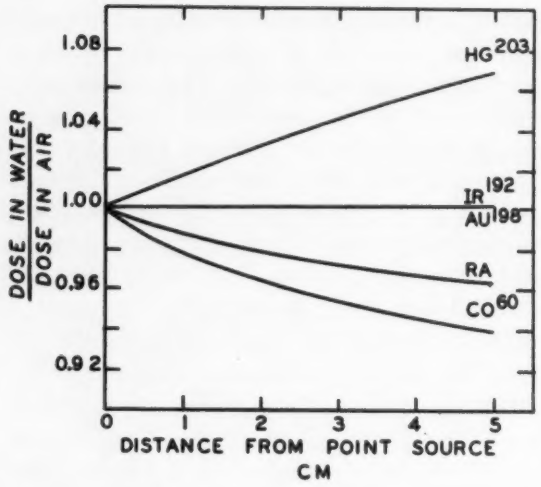

FIG. 4. Water–air dose rate ratio for specific radioisotopes as a function of distance from a point source.

distribution near the source caused, for example, by varying mechanical details in the construction of radium and Co^{60} needles have not been considered.

The data of Figure 3 were used to compute the water–air dose rate ratio for several specific isotopes: Hg^{203}, Ir^{192}, Au^{198}, radium, and Co^{60}. The results are shown in Figure 4. The energy and probability data for radium were taken from Evans.[2] The gamma-ray intensities were corrected for 0.5 mm. Pt filtration using the attenuation coefficients of White.[10] The calculation for Ir^{192} was carried out using the decay scheme data of Baggerly *et al.*[1]* Because of the low energies of some of the Ir^{192} gamma rays, the build-up factor data occasionally had to be extrapolated. The extrapolation, however, could not have introduced an error of greater than 1 per cent into the final result.†

* The method for calculating exposure dose rates is discussed well by Loevinger *et al.*[4] in Radiation Dosimetry.[4]

† The specific gamma-ray emission of Ir^{192} was calculated to be 4.6 r/mc-hr. at 1 cm. This value is somewhat lower than the value of 5.5 r/mc-hr. at 1 cm. quoted by Oak Ridge National Laboratory.[5] The decay scheme of Baggerly *et al.*[1] agrees well with earlier independent measurements reported by the same laboratory.[6] The absolute value of the specific gamma-ray emission, however, will not greatly affect the results of Figure 4, because the specific emission is a constant that appears in both the numerator and denominator of the water-air dose rate ratio. In practice, the uncertainty in the specific gamma-ray emission of Ir^{192} can be circumvented by expressing the source strength in terms of "equivalent milligrams" based on air exposure dose rate measurements.

Some experimental results have been reported that can be used as checks point on the accuracy of the calculations. Recent investigations are those of Van Dilla and Hine,[9] Wootton, Shalek, and Fletcher,[11] and Ter-Pogossian, Ittner, and Aly.[8] All these experiments were performed in water phantoms that were effectively infinitely large and the calculated values also apply to a source in an infinitely large scattering medium. The results of these investigators are compared with the results of this paper in Table II. It is seen that the agreement is generally good. The computed results are about 3 per cent higher on the average than the experimental values.

SUMMARY

Various radioactive isotopes are currently used in place of radium for interstitial therapy. Dose estimations for distributions of these isotopes can be made with standard radium dose-rate tables if two corrections are applied.

The first factor corrects for the difference between radium and other isotope dose-rate in air, and is the ratio of the specific gamma-ray emission constants (r per mc-hr. at 1 cm.).

TABLE II

COMPARISON OF CALCULATED WITH EXPERIMENTAL CORRECTION FACTORS

Author	Isotope	Distance cm.	Result Calculated/Experimental
Van Dilla and Hine[9]	Hg^{203}	2.8	1.00
	Au^{198}	3.6	1.01
	Ra	3.7	1.02
	Co^{60}	3.6	1.02
Ter-Pogossian *et al.*[8]	Ra	2.0	1.03
	Ra	4.0	1.03
	Ra	5.0	1.04
Wootton *et al.*[11]	Co^{60}	4.0	1.02
	Co^{60}	5.0	1.04
	Ra	4.0	1.03
	Ra	5.0	1.05

The second factor corrects for the difference in the absorption and scattering in tissue of the gamma rays of radium compared with the other isotope.

In an evaluation of the magnitude of the second factor as a function of the gamma-ray energy and the distance from the source, which may be done from published data, it is shown that the correction factor is less than 10 per cent for gamma-ray energies of 0.25 to 2.0 mev., and for distances within 5 cm. of the source. Since this range includes all cases likely to occur in clinical practice, the correction factor probably can be neglected for practical purposes.

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RADIATION HAZARDS ASSOCIATED WITH USE OF THE STRONTIUM 90 BETA APPLICATOR*

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IN A recent paper[2] published from this institution, a simplified method of determining the depth dose distribution in a phantom for a strontium 90 beta applicator was described, utilizing a film technique. The method followed closely that employed by Tochilin and Golden.[4] This type of applicator is used with increasing frequency both for the treatment of ophthalmologic lesions and for radiobiologic experiments. Approximately 200 physicians have been currently licensed to use strontium 90 beta medical applicators.[1] These applicators contain from 40 to 100 millicuries of strontium 90, producing dose rates of from 40 to 100 rep per second at contact.[3] It is because of these extremely high dose rates that some hazards may be present during the application of such devices unless proper precautions are taken. The Isotopes Division of the Atomic Energy Commission has drawn attention to these possible hazards in a recent publication.[3]

The film technique referred to above seemed to be a simple and practical method of gauging the possible hazards during the use of the strontium 90 beta applicator.

PROBLEM

The following are some circumstances under which overexposure may occur:

A. Since much of the use of this type of applicator is in ophthalmology, there is a possibility of local overexposure from scattered beta radiation should the physician unwittingly use his hand for retraction of the eyelids.
B. During handling of the applicator while not in actual use there may be significant exposure to nearby personnel in a direct line with the active end of the instrument, again from unscattered or scattered beta radiation.
C. After being replaced in the storage box, there may be a significant exposure from bremsstrahlen if the box is stored on a desk. The bremsstrahlen arise from the stopping of the energetic beta particles by the metal shield in which the active end of the applicator is stored (Fig. 1).

In order to determine whether actual hazard exists, the following experiments were carried out with a strontium 90 source which has a dose rate of 40. rep/sec. at contact.

METHOD

Minimal extra-fast, double-coated, blue base, safety dental film was used throughout the procedure. This film was exposed to a 10 mg. radium needle for varying intervals of time in order to have a film calibration series covering a range from 50 to 300 mr in steps of 50 mr, and from 300 to 2,000 mr in steps of 300 mr. These films were used as the standards for visual comparison with the unknown exposures. For this work the precision of a densitometer was not required, and all comparisons were made by eye. These comparisons were made independently by several observers with consistent findings.

A. The first experiment was designed to measure the extent of lateral scatter of beta radiation when the applicator is in contact with a phantom made of wax, to simulate the conditions of ophthalmologic use (Fig. 2). In order to provide a scattering agent, a block

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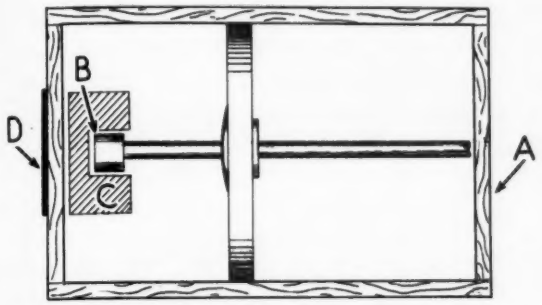

Fig. 1. Schematic drawing of storage box for strontium 90 applicator. (A) Box. (B) Active surface of applicator. (C) Metal shield in which active end of applicator is stored. (D) Position of film to determine maximum bremsstrahlen output.

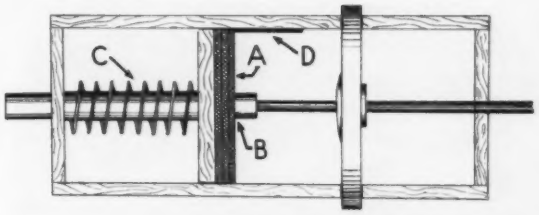

Fig. 2. Arrangement for measuring beta radiation scattered laterally by wax phantom. (A) Block of dental wax 1.5 cm. thick. (B) Active surface of applicator. (C) Spring to push wax firmly against applicator. (D) Film placed 2.5 cm. from the midline of the active surface of applicator.

of dental wax 1.5 cm. thick (Fig. 2, A) was placed in contact with the active surface of the applicator (Fig. 2, B). The spring mechanism (Fig. 2, C) held the wax firmly in place. The film (Fig. 2, D) was placed 2.5 cm. from the midline of the active surface of the applicator. Exposure was initiated by the removal of lead overlying the film, and was terminated by removal of the applicator.

B. In order to determine the forward attenuation of the beta particles in air, films were placed perpendicular to and in direct line with the active portion of the applicator at distances up to 100 cm.

C. The applicator storage box is represented schematically in Figure 1. The applicator is stored by placing the active surface (Fig. 1, B) within the metal shield (Fig. 1, C). As mentioned previously bremsstrahlen are generated when the beta particles are stopped by the shield material. The level of radiation due to this was measured by placing film (Fig. 1, D) flat on a face of the storage box as shown. The films were exposed for various times.

RESULTS

A. The dose rate due to the laterally scattered beta radiation at the position 2.5 cm. lateral to the applicator head, with the wax scattering medium in place, was found to be 6 rep/minute. This value may be contrasted with 1.5 rep/week to the hands, which is officially adopted as the maximum by the National Bureau of Standards.

The film placement with respect to to the source and the wax scattering medium is shown in the drawing (Fig. 3), with the arrows (a) and (b) indicating the film. Figure 4 is a print of a typical exposed film. The region (a) in both Figures 3 and 4 represents that portion of the film that had been exposed to the beta particles that

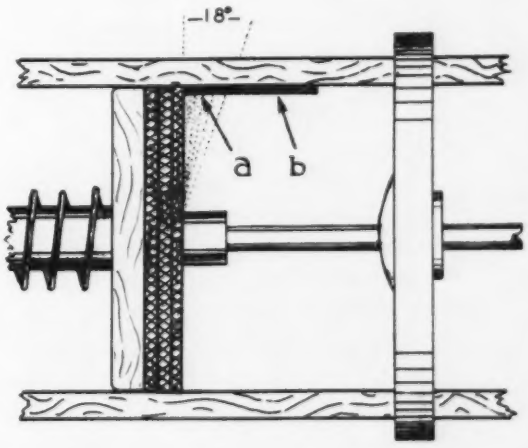

Fig. 3. Exposure of film due to beta radiation scattered laterally by wax phantom. (a) Portion of film exposed to the beta radiation. (b) Relatively unexposed area of film. Beta rays backscatter as much as 18 degrees from plane of wax in this case.

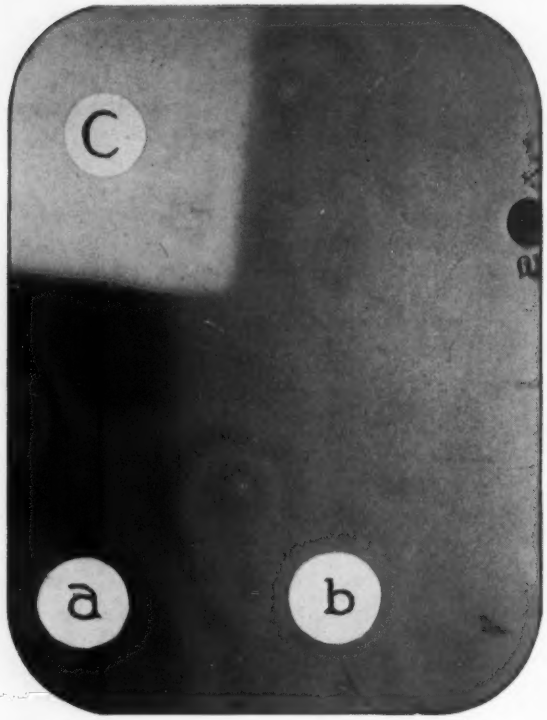

FIG. 4. Print of film exposed as shown in Figure 3. (a) Exposed portion. (b) Relatively unexposed part of film. (c) Unexposed corner covered by a lead marker to determine film's orientation.

were backscattered from the wax. In this case the beta particles backscattered as much as 18 degrees from the plane of the wax. Region (b) is the portion of the film that was relatively unexposed to the beta radiation. The unexposed corner (c) in Figure 4, had been covered by a lead marker to determine the film's orientation.

B. The films placed in a direct line with the active surface, in order to measure the forward attenuation in air, showed a dose rate of approximately 50 mrep/minute at a distance of one meter or 600 mrep/minute at one foot.

C. Contrary to the manufacturer's stated dose rate of 10 mr/hr. due to bremsstrahlen at the face adjacent to the shield in the storage box, this experiment showed the dose rate to be approximately 500 mr/hr. Confirmation of these film results was obtained by using either a Geiger-Müller tube or an ionization chamber, and by extrapolating the current readings to the surface of the box. However, at a distance of one foot from the storage box, the dose rate was about 10 mr/hr.

CONCLUSIONS

These experiments illustrate the potential hazards always present when handling, cleaning and using high energy devices such as the strontium 90 beta applicator. As it becomes more and more ubiquitous in medical installations, adequate consideration should be given to the possibility of overexposure of the operator or adjacent personnel while their attention is being directed toward the patient.

Familiarity with these instruments should breed increased respect; the active area should be shielded at all times when not being cleaned or in use; and the added protective factor of distance should be utilized when the instrument is not in use.

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SOME ASPECTS OF SUPERVOLTAGE RADIATION THERAPY*

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ONE of the most striking advances in the field of radiation therapy during the last decade has been the great increase in the availability and use of roentgen and gamma rays generated at more than 1 million volts—the so-called supervoltage or megavoltage radiations. Now we have, in forms suitable for clinical use, the resonant transformer[2] and Van de Graaff generators,[16] a variety of radiocobalt telecurie units,[1,5,9] the linear accelerator,[12] the betatron[11] and the synchrotron.[4] Thus there are, readily available for clinical therapy, machines capable of generating radiation at voltages from 1 million up to 30 million volts or even higher.

Considerable numbers of these machines are now in use and many radiotherapists are contemplating entry into this field. It therefore seemed appropriate to examine the properties of supervoltage radiation to see what advantages it offers to the radiotherapist, to consider whether there is an optimum energy level and if so, which machine is likely to be most effective.

The first, and obvious, advantage of this type of radiation is in percentage depth dose, which, as shown in Figure 1, increases rapidly when we go from 250 kv. into the supervoltage range. It continues to increase, though more slowly, above 20 million volts for even at these energies pair production plays a very small part in the attenuation of the beam in water or soft tissue. Since increase of depth dose enables a particular treatment to be given with a smaller number of fields or with a smaller dose on each field than is necessary at 250 kv., supervoltage treatments may well, on the one hand, be simpler and, on the other, have a smaller systemic effect upon the patient because of lower skin and integral doses. From this point of view, therefore, the higher the generating voltage, the better.

The second advantage is in the much smaller scattering suffered by supervoltage beams. This not only reduces the total skin dose, but it also means that there is far less radiation outside the geometric confines of the beam. Thus, not only is the integral dose for any given tumor dose smaller than in 250 kv. therapy, with a consequent reduction in the general systemic effect upon the patient, but, also, vital tissues and organs lying close to but outside the main beam will suffer less damage and therefore are better able to play their part in the recovery of the patient. It must be noted, however, that to exploit this advantage to the full, the treatment beam must have the minimum of penumbra. This calls for well-designed field limiting diaphragms and also for the smallest possible focal spot.

It will be noted that in Figure 1, the percentage depth doses are expressed in terms of the maximum dose rather than of the surface dose, as is customary at 250 kv. This is advisable because of the so-called "build-up" of ionization which occurs below the surface with supervoltage radiation, and which constitutes a third advantage of these rays over those at lower energies. The primary electrons set in motion by high energy photons travel in a predominantly forward direction with ranges, in soft tissue, of upwards of several millimeters. Since these particles produce most ionization at the end of their tracks, the ionization (or dose) due to a supervoltage beam reaches a maximum some distance below the surface. The depth of this maximum increases with the energy of the rays, as shown in Figure 2, while the

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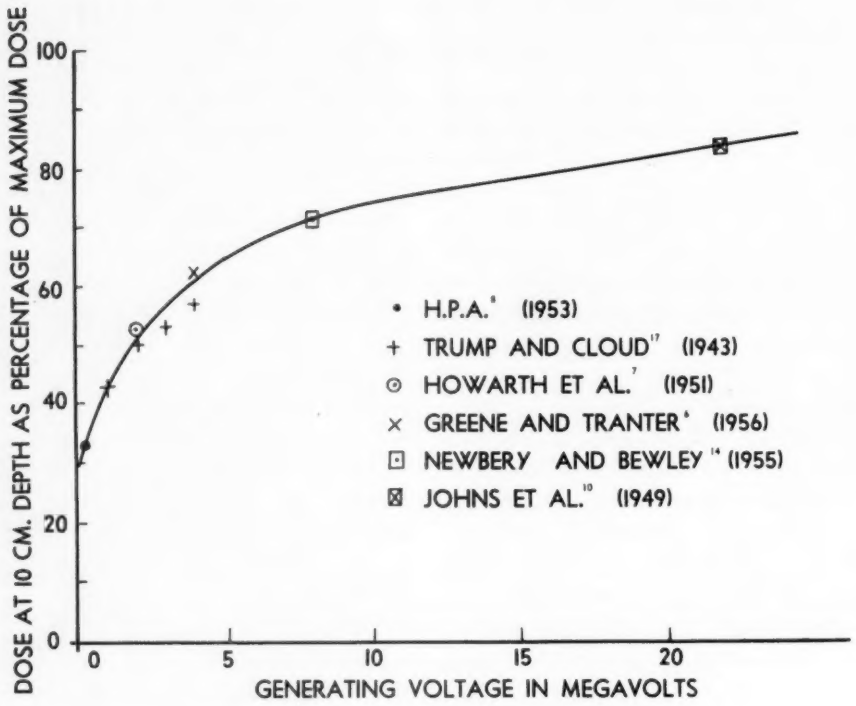

FIG. 1. Variation of D_{10} with generating voltage.

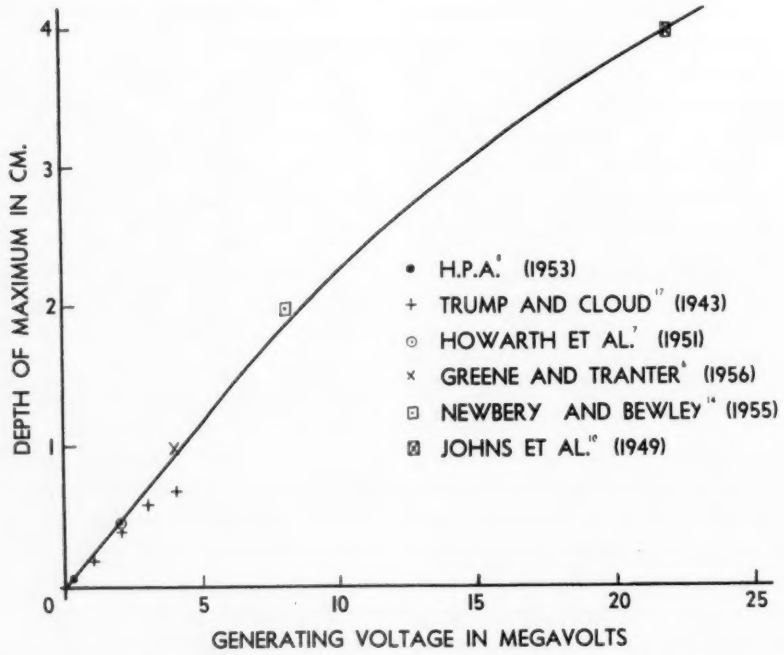

FIG. 2. Variation of depth of maximum dose with generating voltage.

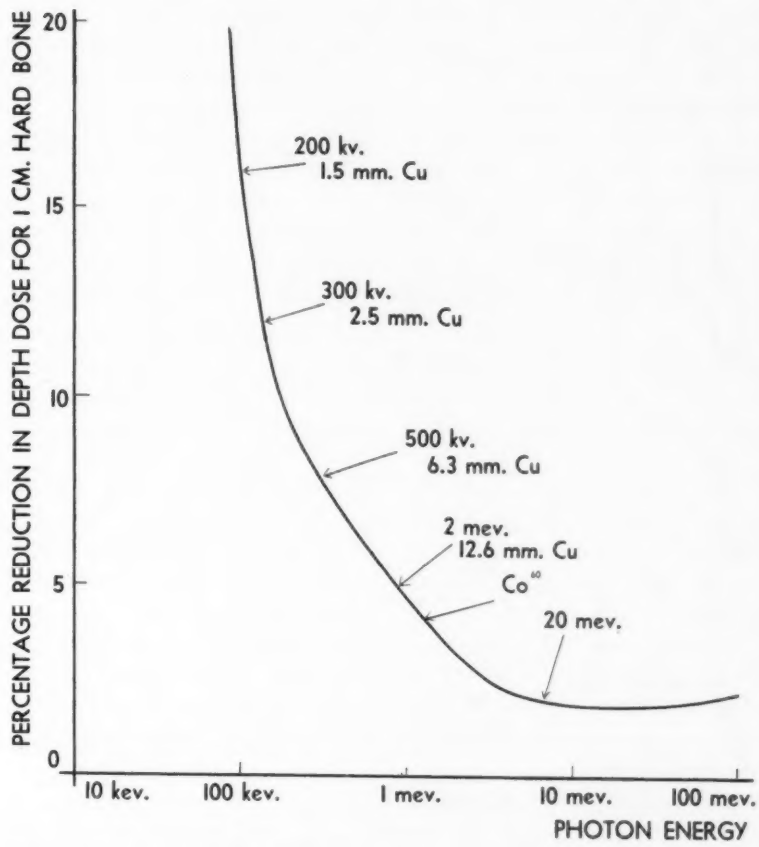

Fig. 3. Variation of shielding effect of 1 cm. of bone with photon energy.

percentage surface dose falls progressively, especially as the amount of backscatter is very small. The surface dose for a 4 million volt roentgen-ray beam, for example, is only about 25 per cent of the maximum dose, which occurs approximately 1 cm. below the surface.

Thus, provided there is no material across the beam within about 30 cm. of the surface, the skin dose—and hence the skin effect—will be very small. It does mean, of course, that in general, closed ended applicators are ruled out, and that skin reaction is completely misleading as a guide to radiation effect. However, these are but minor drawbacks compared with the great increase in the patient's comfort, an advantage which grows as the generating energy is raised.

The data so far presented have been obtained from measurements made in water or similar material and apply closely to soft tissue. The distribution of the radiation dose within a patient will, however, be different from that in water because of the presence of other tissues of different density and atomic number, notably lung tissue, fat and bone. Because of its higher density and atomic number, bone absorbs more radiation energy than would an equal thickness of soft tissue. Therefore a layer of bone will, to some extent, shield from the irradiating beam tissues lying beyond it. Figure 3 shows how the shielding effect of hard bone—expressed as the percentage excess absorption which occurs when 1 cm. of hard bone replaces 1 cm. of soft tissue—changes with photon energy. The superiority of supervoltage radiation in this respect is quite obvious and it will be clear that central depth dose values and isodose curves prepared from measurements in,

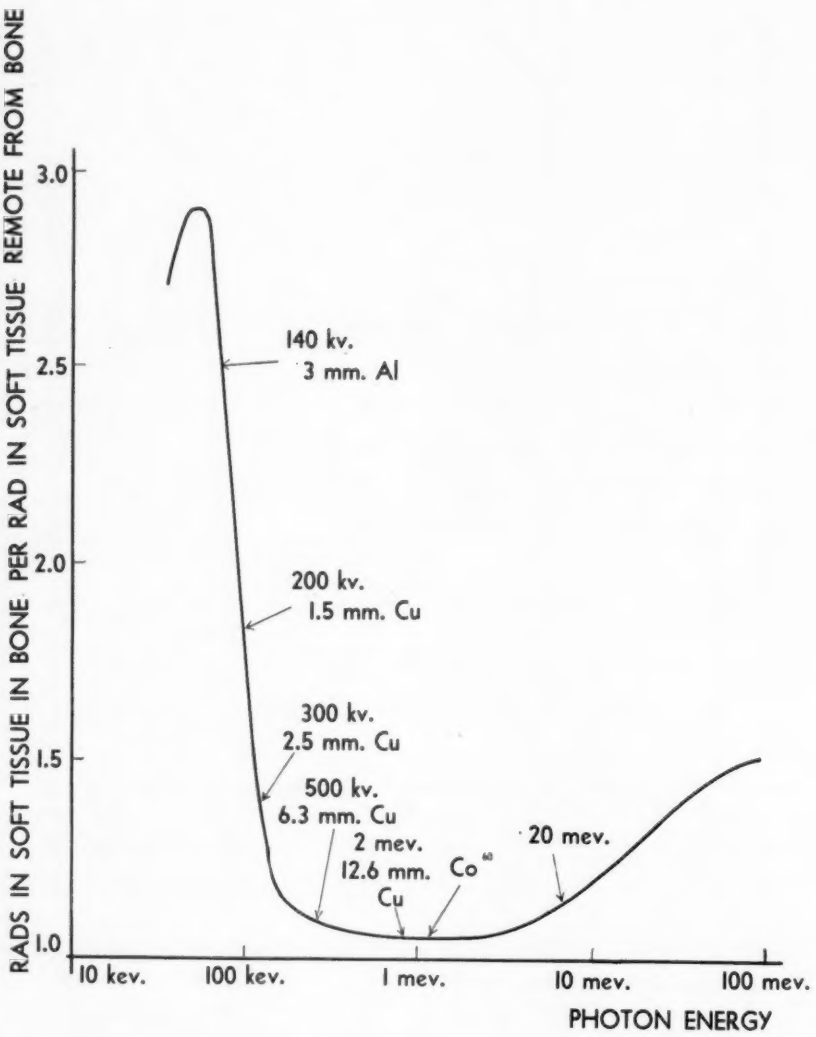

FIG. 4. Variation of dosage in soft tissue elements in bone with photon energy.

say, a water phantom, are more exactly applicable to the patient for higher energy radiations than they are for 250 kv. radiations.

When we consider the radiation dose received in the bone itself, we find a similar but modified state of affairs. As far as radiation effect is concerned it is the energy absorbed in the soft tissue elements in bone (the haversian system), or that absorbed by soft tissues growing close to the bone rather than the absorbed dose in the inorganic bone matrix, that is important clinically.[15] These soft tisues will receive an increased flux of electrons due to their proximity to bone but the dose they receive, relative to that received by soft tissues distant from bone, is, at the lower voltages, considerably tempered by the shortness of the range of the electrons. Spiers[15] has shown, for example, that though for a photon energy of 100 kev. hard bone absorbs 3.7 times as much as soft tissue, the haversian system receives only 2.4 times the dose received by soft tissue remote from bone. Nevertheless, the disparity between the dose in bone and that in soft tissue is dramatically reduced by using high energy radiation, as is shown in Figure 4, and this reduction constitutes a further and major advantage of supervoltage therapy.

So far, therefore, it would appear to be advantageous therapeutically to use radiation of the highest possible energy. However, a further study of Figure 4 reveals the first of a number of reasons why very high energy rays are not therapeutically desirable. For photon energies above 4 or 5 mev., increasing pair production in bone reverses the downward trend of the curve and thereafter the relative energy absorbed in bone increases again. Now, however, the range of the secondary electrons is considerable and the alleviation found at lower energies no longer occurs. Therefore, the dose received by soft tissues in or near bone increases again with increasing energy and though the increase is certainly unimportant up to the energy of radiations from a 20 million volt betatron, it constitutes a cogent reason against the therapeutic use of extremely high energy radiation.

Nor, when one examines the situation further, is the increase of percentage depth dose with energy an unmixed blessing. The physical factors already enumerated reduce the dose at the surface through which the beam enters the patient, but the increasing penetration raises the dose at the exit surface. It is thus not difficult to imagine a situation which, because of this exit dose increase, transfers skin reaction problems from the entrance to the exit side. Indeed, users of supervoltage apparatus working at only a few million volts are familiar with the phenomenon of a reaction on the distant side of the patient when there is no visible effect on the entrance side. While it is difficult to lay down a strict criterion for judging this matter, an attempt is made in Figure 5 to indicate the order of the effect. There is shown, for both entrance and exit surfaces, the way in which the ratio of the surface dose to the tumor dose changes as the radiation energy is increased. For the sake of this diagram, the tumor is assumed to be 10 cm. deep and the exit surface a further 10 cm. beyond. It will be clear that best skin dose conditions are achieved as around about 3 to 10 million volts and that while the rise in exit dose at high energies is not dramatic, nor is it likely to be a factor grossly limiting any treatment, it is something to be avoided unless there are outweighing advantages in other directions in using the higher energies.

A further disadvantage of the use of very high energy radiation lies in the narrowness of the beam of useful intensity, the angle of which decreases as the energy increases. Because at high energies the radiation is sharply concentrated in the approximate direction of the producing electron stream, it is necessary to introduce "beam flatten-

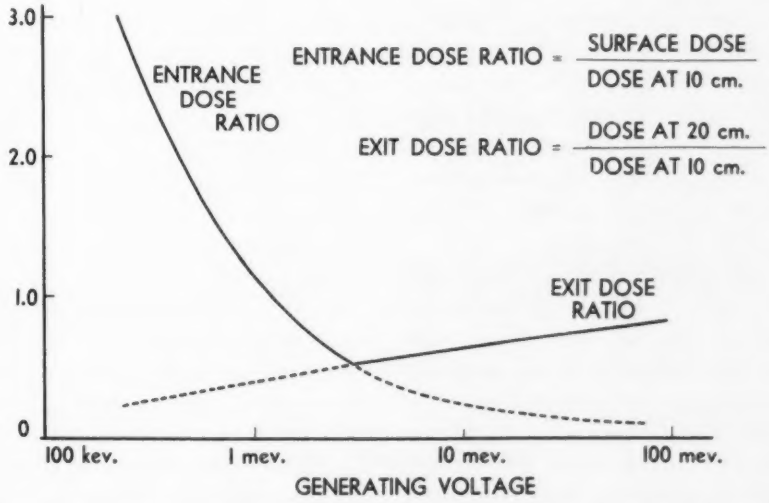

Fig. 5. Variation of ratio of surface to tumor dose (taken as at 10 cm. depth) with generating voltage.

ing" filters, with consequent loss of output, to produce a clinically satisfactory radiation distribution across the beam. Thus, to obtain a uniform beam 30 cm. in diameter at 100 cm. focus distance with a 4 million volt linear accelerator, the compensating filter required reduces the central intensity by 33 per cent. At higher energies, if an economic output is to be retained, the size of field covered is much reduced. For example, on the 20 million volt betatron, even with "flattening" to the 50 per cent level, *i.e.*, losing half the central intensity, the maximum diameter of uniform field is of the order of 15 cm. at 100 cm. focus distance. Under comparable conditions at 50 million volts the maximum field would be only 6 cm. in diameter.

Finally, it is of some importance to remember that, in general, the higher the energy the larger, the more cumbersome, and the more expensive the apparatus and also the greater the amount and cost of protection that will be required.

In summary, therefore, we may say that supervoltage radiation offers the radiotherapist marked advantages over that generated at 250 kv. However, while increasing energy gives continuous advantages in depth dose, entrance dose and bone shielding, it eventually introduces disadvantages in respect to exit dose, bone absorbed dose and beam shape, and furthermore it poses new operational problems since the machines are more difficult to use clinically because of their bulk. A careful weighing of all these factors suggests that the optimum generating voltage for supervoltage radiation therapy is somewhere around 5 million volts, and certainly within the range of 3 to 8 million volts.

There now remains the question of the most suitable machine for the provision of this radiation. It is beyond the range which can be conveniently dealt with by the machines using direct voltage production and below the energy at which the cyclic accelerators work most efficiently. The available alternatives are, therefore, the radiocobalt telecurie units (which can be considered as equivalent to 3 million volt roentgen-ray machines) and the linear accelerator.

The former have the considerable advantage of requiring no generating apparatus, of having a nonfluctuating output of radiation, and of requiring very little technical attention, at least in respect to the radiation beam. It must not be forgotten, however, that the source strength is continuously waning, and with it, the radiation output. Furthermore, the telecurie cobalt unit has a large source diameter which, by the penumbra it produces, vitiates one of the great advantages of supervoltage beams —the small amount of scattered radiation.

On the other hand the linear accelerator has a small focal spot (5 mm.) and hence a very small beam penumbra, a considerably higher output (120 r per minute at 1 meter is easily attained at 4 million volts, as compared with about 40 r per minute from 2,000 curies of radiocobalt) and even at 4 million volts has distinct advantages in terms of depth dose, skin dose, bone shielding and bone absorbed dose. These advantages can be increased by going up to 5 or 8 million volts, generating energies of which the accelerator is readily capable. Nor must too much stress be placed upon the reliability of the radioactive source. In spite of its revolutionary design, the linear accelerator has proved, at the Christie Hospital and elsewhere, to have a remarkably steady roentgen-ray output, to need very little more technical attention than a conventional 250 kv. apparatus, and to be very reliable. The average treatment time lost due to faults of all kinds is just under two days per year,[13] which compares very favorably with the record of the radiocobalt units.

In the last resort, the choice of machine for a given department may well depend on financial considerations. The linear accelerator is the more costly machine and calls for a larger room with thicker protective walls. On the other hand it can treat considerably more patients in any given time—12 fields per hour is well within the

capacity of our 4 million volt machine. In a recent survey Flanders[3] (1953) estimated, for several different types of supervoltage machines, the cost of giving a treatment of 5,000 r at 10 cm. depth to a patient, assuming that each machine was working to its full capacity. Allowance having been made for capital depreciation on the cost of the machine and the treatment and apparatus rooms, the cost of spare parts or source replacement, and the salaries of the technical staff required, the cost for a telecurie cobalt unit and for a linear accelerator was almost identical.

Thus, although the radiocobalt telecurie unit has a place in a small radiotherapeutic center, or when technical assistance is difficult to obtain, there seems no doubt that the linear accelerator operating in the region of 4 to 8 million volts is the best available machine for supervoltage roentgen therapy.

SUMMARY

The advantages of supervoltage radiation over that generated at 250 kv. are its increased percentage depth dose, decreased surface dose and scatter, the increased penetration of bone and its reduced dose to the soft tissue elements in or near bone. While some of these advantages increase progressively with increasing generating energy, others—and especially the last—attain a maximum and then this decreases for still higher energies. After considering all factors, it is concluded that the optimum generating voltage for supervoltage radiation therapy is 5 million volts and that the best apparatus for achieving this is the linear accelerator.

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THE DOSE-TIME RELATIONSHIP IN RADIATION THERAPY: HIGH DOSE, PROLONGED TIME, LARGE VOLUME RADIATION THERAPY; THE LIMITS OF TOLERANCE*

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THIS is a preliminary report of problems of dose-time relationship as studied in a limited number of cases of extensive cancer of the upper respiratory passages, the oral cavity, and pharynx. The patients in the study were treated to tumor exposure dose levels of 8,000 to 10,000 r with 2 mev. roentgen rays delivered over periods of eighty to one hundred days. The aspects of dosimetry, the radiation effects on both normal and neoplastic tissues, and the general physical and psychologic tolerance of patients are considered. This study was undertaken to determine whether or not prolongation of the over-all radiation treatment time and the administration of a dose appropriate to the over-all treatment time might result in a greater cancerocidal effect and a diminished normal tissue effect.

THEORETIC CONSIDERATIONS

Certain theoretic considerations developed in previous studies[1] suggested that the dose-time plot could be extended beyond treatment times and doses generally employed and that differential effects on cancer, on skin, and possibly on other normal tissues might appear. Kiga,[9] in other theoretic studies, has postulated that in a cell there are a certain number of molecules essential to the continued existence of the cell and that the cell can survive if no more than a certain fraction of these are damaged by radiation. The number of these essential molecules damaged is proportional to the dose of radiation. Conversely, if this fraction of damaged molecules is exceeded the cell dies. Thus, survival can be expected to be a function of dose and the relationship:

$$\frac{m_d}{m}=f(D)$$

obtains where m is the number of molecules essential to the continued existence of the cell; m_d the number damaged, and D the dose.

Certain of these damaged molecules, m_d, essential to the continued existence of the cell may, however, become reconstituted or "recover." This seems to be a capacity related to biologic phenomena in general and the net number of damaged molecules is:

$$m_d - m_r$$

where m_r is the number of molecules reconstituted or "recovering." It is to be noted that the relationship $m_r \not> m_d$ obtains and that recovery may not be complete. The net change, then, in the ratio of permanently damaged to essential molecules is:

$$\frac{m_d-m_r}{m}.$$

In biologic material recovery is a function of time, t, and the relationship:

$$\frac{m_d-m_r}{m}=f(t) \text{ also obtains.}$$

Finally, then,

$$\frac{m_d-m_r}{m}=f(D, t).$$

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In human cancer therapy one would like to attain the relationship for the relative effects of radiation on tumor cells and on normal cells of:

$$\frac{m_d - m_r}{m \text{ (tumor)}} > \frac{m_d - m_r}{m \text{ (normal)}}.$$

Inasmuch as these effects are, in part, functions of dose, it follows that the attainment of a differential effect will depend, in part, upon the attainment of a high technical or efficiency factor[2] in planning the application of the radiation.

But these biologic response ratios are not functions of dose, alone, for they are also, as indicated above, functions of time. Many other but unknown variables are probably inherent in the biologic materials themselves and these cannot, in the present state of clinical radiation therapy, be clearly defined or quantitatively evaluated.

While the radiosensitivity of a given individual cell may be greatest at a particular stage of mitosis, it is impossible to irradiate all of the cells of a population of cells at this particular stage unless they are dividing synchronously. This condition does not obtain in complex biologic material and one could not expect, therefore, to deliver radiation to all of the cells at their most radiosensitive stage. This may be an important reason why it has never been conclusively demonstrated that significant differential tumor and normal tissue responses appear when treatment times are varied. The skin response may be an exception to this general statement. While, therefore, the biologic response ratio developed above is necessarily a function of time, this may be a very subtle relationship when dealing with populations of cells.

Melnick and Bachem[11] have suggested that the type of damage sustained by a cell when irradiated may vary according to whether the cell is irradiated with a large single increment or multiple small increments of dose applied over a long period of time. In the first instance primary necrosis of the cell occurs, while in the second instance the chromosomes are altered in such a way that the cells are transformed into abnormal forms which become either giant cells or multiply abnormally for, presumably, a limited number of generations. This latter effect may be a more fully cumulative one and on a theoretic basis it might be more desirable to accomplish a tumor lethal effect by extension of treatment time rather than by a single large increment of dose.

Clinical experience indicates that for the production of a given radiation effect in at least some human tissues or human neoplasms a parabolic relationship exists between dose and time in conformity with the equation:

$$D = kt^n$$

where D is the total dose in t days required to produce the given radiation effect; k is the dose required to produce the given effect when the dose is applied as a single radiation (it is a measure of the average radiosensitivity of the tissue and is termed the radiosensitivity constant); t is the treatment time in days; and n is a positive fraction related to recovery rate. Whereas for a particular cell the biologic response ratio, $(m_d - m_r)/m$, may vary as a function of the time cycle in which the cell is irradiated, the radiosensitivity constant, k, is simply the average radiosensitivity of the cell population, or tissue, and it is a function of dose. As a clinical phenomenon this variation of average radiosensitivity of tissues is most strikingly demonstrated when the infantile thymus is irradiated with a single small dose. This is the aspect of radiosensitivity associated with the constant, k. The other, biologic aspects of radiosensitivity are subtle and at present poorly understood. They are related, for want of better understanding, to the mitotic cycle of the individual cell.

The classic experiments of Regaud and Ferroux[13] showed that susceptibility to a certain kind of damage was altered when the conditions of irradiation in respect to time were changed. Likewise, the relative radiosensitivities of two different tissues irradiated under one set of conditions were altered when the conditions were changed.

Certain evidence developed by Du Sault[5] suggests that other differential tissue effects may be observed as the over-all treatment time is varied but these effects are, at best, subtle. The exponent, n, of the dose equation relates the effect of over-all treatment time to these possible differential tissue effects. The response relationship:

$$\frac{m_d - m_r}{m} = f(D, t)$$

takes into account possible biochemical and biologic mechanisms in producing the response and relates this response to total dose and over-all treatment time. It does not take into account the variation in the radiosensitivity of a particular cell related to its mitotic cycle and there is no presently known way to equate this.

DOSIMETRY

It is very difficult to know precisely what to call tumor or tissue dose when dealing with an irregularly infiltrative and indefinable tumor existing both within and outside of an irregular cavity with air and tissue interfaces and all contained within a larger volume of irregular shape, the head. Whether rotational or fixed field therapy is used, one is accustomed to thinking in terms of the ideal shape and a homogeneous medium. Neither is very near the fact. In addition, in the ordinary graphic solution of a dose distribution problem, generally only an arbitrarily chosen, or average, two dimensional cross section is selected and a three dimensional volume distribution is not ordinarily constructed. In addition, volume dose is generally neither computed nor related to tumor or tissue effects. On the other hand, if the high energy machines presently available for therapeutic radiology are to be fully and correctly exploited because of their capacity to deliver high tumor doses, then the whole matter of volume dose effect, especially in relation to radiation effects in normal critical tissues, must be explored.

The initial study of a dose distribution problem in the treatment of cases such as are considered here generally commences with a preselected cross section of the patient which is drawn to size; the tumor bearing area is identified; and isodose curves are plotted. In the case of rotational therapy the nomograms of Trump and his coworkers[14] have been applied. Where possible, calculations have been checked by cavity ionization measurement in the oral and pharyngeal cavities. There has been good correlation between such measurements and the doses as determined graphically from isodose plots or estimated from the nomograms. Where discrepancies existed, the cavity ionization dose was recorded, in terms of percentage of the axis air dose, as the tumor dose. Photographic dosimetric studies using films sandwiched in a pressdwood phantom carved to the shape of the Eycleshymer and Schoemaker[6] sections have shown that in general there is a gradient of only about 10 per cent between the maximum dose at the axis of rotation and the surface of the cylindric volume or sphere defined by the beam. This has a very significant implication for it means that for large fields large volumes of tissue are subjected to more or less uniform high doses.

Chemical dosimetry provides a means for the exact determination of the average dose throughout a given volume, for the given volume can either be defined by containing it or by measurement or calculation of the actual volume exposed to radiation. A plastic shell head phantom conforming in size and shape with the pressdwood phantom was prepared as a container for the chemical solution. Isolated inserts containing the sensitive solution were made of appropriate size and shape to simulate tumor and were introduced into an appropriate place in the phantom. The head phantom itself was filled with the sensitive solution and set up precisely before the roentgen-ray beam to simulate specific treatment conditions. The portion of the head phantom irradiated could be determined by inspection and the fluid contained within the limits of the roentgen-ray beam

could be measured. The irradiated portion of the solution diffuses throughout the total volume of solution in the head phantom, but by making appropriate calculations the volume dose for the volume of solution irradiated may be derived. This method may be thought of as permitting an experimental determination of the absorbed dose and it makes possible a highly accurate comparison of average volume doses for a variety of field sizes and irradiation conditions including those conditions of irradiation precisely simulating human patient irradiation. In addition, small volumes of solution may be contained in shapes simulating actual tumor and volume doses accurately determined.

The results of such volume dose studies show that the average volume doses in the normal tissues traversed by the beam are great in respect to the average volume doses in the tumor bearing regions. In the case of a large (90 cm.^{2}) field, the ratio of the latter to the former is not better than 3 to 1. This means, of course, that the entire irradiated volume is being subjected to high doses and this accounts, in part at least, for the severe reactions observed. Exposure doses* (D, in roentgens) were given conforming with the equation:

$$D = kt^n$$

where $k = 2{,}750$ and n was given a range of values between 0.21 and 0.28. Total tumor exposure doses varied from 8,000 r given in eight days to 10,000 r in one hundred days. In general, treatments were given three times weekly.

* Absorbed dose in rads may be derived by multiplying exposure dose in roentgens by the appropriate factor (f). (From "Methods of Calculating the Absorbed Dose from Measured Ionization." In preparation, National Bureau of Standards, 1956).

Photon Energy mev.	f		
	H_2O / air	bone / air	muscle / air
.90 (Av. energy 2 mev. Van de Graaff)	.974	.928	.965

CLINICAL STUDY

The present clinical study was undertaken on the basis of the preceding theoretic considerations and for the purpose of exploring the effects of ionizing radiations on human malignant neoplastic and incidentally irradiated normal tissues treated over periods of from eighty to one hundred days. The case material was composed of 13 selected patients with either inoperable or extensive and inoperable cancer of the upper respiratory passages, the oral cavity, and pharynx. The irradiation was limited (with the exception of 1 case of supplemental radium needle implantation of the neck) to external roentgen therapy with a 2 mev. Van de Graaff generator. Rotational, either complete or segmental, or fixed field techniques were employed as seemed to be appropriate to the individual case. Pertinent details concerning these 13 cases are shown in Tables I, II, and III.

It is evident from a perusal of Table III that the results in this small group of cases have been poor. Whether this is a reflection of the already advanced state of the cancers in most of the the patients seen or of the treatment employed is not determined by this study. The study has not been evolved to determine curability rates for different types of cancer for such a study requires larger series and time. The study does concern itself with immediate effects and with attempts to evaluate these effects, the limits of tissue and patient tolerance, and what could be considered an optimal or reasonable relationship between dose and time for the prolonged treatment time employed. The study was also evolved to provide some indication as to whether the prolonged treatment time, with appropriate doses, resulted in any better tumor or normal tissue effects.

Immediate mucosal radiation reactions were not diminished in either severity or duration by the prolonged irradiation time nor were there cyclic variations as reported by Friedman[7] for shorter irradiation times. In fact, the reactions were in general extremely intense in those patients where the

TABLE I

PATIENT IDENTIFICATION

Ref. No.	Initials	NIH Clinical Center No.	Sex	Age (yr.)	Diagnosis (carcinoma of)	Duration (mo.)
1	C.W.	01-07-63	M	52	oropharynx	3
2	J.C.	01-07-78	M	8	antrum	2
3	W.M.	01-08-99	M	13	nasopharynx	7
4	J.C.	01-02-63	M	72	tongue	24
5	E.L.	01-16-32	F	69	antrum	4
6	M.M.	01-20-83	F	59	oropharynx	7
7	W.S.	01-24-05	M	67	laryngopharynx	6
8	H.P.	01-27-06	M	35	tonsil	5
9	C.W.	01-31-23	M	86	tongue	36
10	C.A.	01-30-16	M	75	tongue	48
11	O.D.	01-47-22	M	71	antrum	12
12	I.F.	01-47-91	F	27	nasopharynx	2
13	W.McC.	01-53-06	M	70	tongue	4

TABLE II

CHARACTERISTICS OF LESIONS AND TREATMENT

Ref. No.	Anatomy			Histology[2]	Treatment			
	Primary Site	Neck Extension[1]			Fields[3]		Average Tumor Exposure Dose r	Time (da.[4])
		Right	Left			cm.		
1	Fauces, tonsil, base of tongue, pyriform sinus	5-a	0	E	R seg	6×10	8,000	100
2	Antrum, naris, nasopharynx	0	1?	U	F_3	6× 7	8,000	100
3	Nasopharynx, massive	5-a, 1?	0	LE	F_2	6×10	8,000	100
4	Tongue, fauces, pyriform sinus, recurrent postoperatively	0	0	E	F_2	8×10	8,000	100
5	Antrum, ethmoid	0	0	E	F_3	7× 8	10,000	100
6	Posterior oropharynx, nasopharynx, fauces, epiglottis	1?	0	E	F_2	7×12	10,000	100
7	Pyriform sinus, epiglottis, extrinsic larynx	2, 5-a	0	E	F_2	9×12	9,500	95
8	Tonsil, soft palate, fauces	0	4, 5-a	T	R seg	8×12	10,000	100
9	Anterior two-thirds of tongue, floor of mouth	2	0	D	R	9×11	10,000	100
10	Entire tongue, floor of mouth	2, 3, 4, 5	2, 3, 4, 5	E	R seg	11×11	8,000	80
11	Antrum, ethmoid, orbit	0	0	U	F_3	6× 7	8,000	86
12	Nasopharynx, posterior choana	4-a	4-a, 5	U	R	7× 8	8,000	85
13	Dorsum and base of tongue, floor of mouth	2, 5-a	0	E	R	8×10	8,000	85

[1] Cervical lymph nodes, Code: 0—none palpable; 1—retropharyngeal; 2—submaxillary; 3—submental; 4—superficial cervical, (a) anterior group; 5—deep cervical, (a) superior group, (b) inferior group.

[2] Histology: U—undifferentiated squamous cell carcinoma; D—differentiated squamous cell carcinoma; L—lymphoepithelioma; E—epidermoid carcinoma; T—transitional cell carcinoma.

[3] Fields: R—360° rotation; R seg— <360° rotation, generally excluding spinal axis; F—fixed and number of fields.

[4] Over-all time. Treatments given three times weekly.

TABLE III

RESULTS OF TREATMENTS

Ref. No.	Epithelitis			Complications		Status		Autopsy Findings
	onset[1]	degree	duration	radiation	other		mo.[2]	
1	Late	Intense	Persistent	Intense pharyngeal edema and ulceration	Gastric hemorrhage	Died of disease and complications	5	Persistent cancer of tongue, oropharynx, and lymph nodes
2		Mild		Prompt local recurrence	Intracranial extension	Died of disease	11	Persistent cancer with necrosis. Acute brain abscess
3		Mild		No	Metastases in neck beyond treatment field	Living with disease	22	
4	Early	Intense	Subsided at thirty-fifth day	Persistent edema of tongue and fauces	Aspiration pneumonia	Died after esophagostomy	7	Persistent cancer of hypopharynx, aspiration pneumonia, pulmonary infarcts and metastases
5		Moderate			Persistent pain	Died of massive local hemorrhage	7	No autopsy
6	Early	Intense	Throughout treatment	Intense edema of laryngopharynx		Died of massive local hemorrhage	8	No demonstrable cancer. Extreme metaplasia, edema, and other radiation changes of pharynx. Focal bleeding point not found
7	Early	Intense	Persistent at end of treatment	No		Died of cancer. Regression in neck incomplete	6	No autopsy
8	Early	Intense	Persistent ulcer of tongue	Woody edema of neck, dysphagia, pain	Metastases in neck beyond treatment field	Living with disease	10	
9	Early	Intense	Persistent ulcer and pseudomembrane	Necrosis of tongue	Tertiary syphilis	Died with persistent tumor	6	Extensive persistent cancer in tongue and oropharynx. Myocardial infarction
10	Early	Moderate	Persistent	Very advanced case, poor response	Intrathoracic metastases	Died of metastases	3	Persistent cancer in mouth but marked tumor destructive effects. Cancer in lungs, neck lymph nodes, thyroid and heart
11		Moderate		No	Local infection	Disease uncontrolled in orbit	5	Cancer in orbit. Necrosis of maxilla. Brain and lung abscesses
12		Mild		No	No	Well and no evidence of disease	6	
13	Early	Moderate	Persistent	Extreme edema of tongue and floor of mouth during treatment and subsiding at completion	Esophagostomy	Living. Immediate response fair but probably incomplete	5	

[1] Onset: early—2,000 r tumor dose, or less.
[2] Months after starting treatment.

oral and oropharyngeal cavities were irradiated. The reactions were of only mild or moderate degree in the patients irradiated for sinus or nasopharynx carcinoma. Two factors probably account for this: (1) that when the sinuses and nasopharynx were irradiated the oral and oropharyngeal cavities were not and reactions developing

in the sinuses and nasopharynx are not intolerable to the patient, and (2) that the fields employed in the irradiation of the sinus and nasopharynx cancers were smaller than those used in the oral cavity and oropharynx cases.

There evidently is a high correlation between the severity of the reactions observed and the size of the fields used in either rotational or fixed beam therapy. The average size of the fields in those having severe reactions was 90 cm.^{2} and in those having mild reactions 63 cm.^{2} The average size of the field employed for rotational techniques was 85 cm.^{2} compared with that for fixed fields of 60 cm.^{2}.

Rotational techniques with the exclusion of the spinal axis and with the axis of rotation determined as seemed appropriate for the anatomy of the tumor or two or three fixed fields were employed. Field sizes were selected in conformity with the anatomy of the primary tumor and adjacent extension into the neck. Continuous monitoring of the treatment beam and patient-tumor orientation in both fixed field and rotational roentgen-ray therapy was effected by the use of an image amplifier and closed circuit television.[3]

Tumor response was highly variable. Failure to control the cancer at the presenting sites, complications of the radiation therapy, metastatic cancer, and concurrent disease have accounted for the problems encountered in the management of these generally far advanced cancer patients. In 6 cases the cancer was not controlled even temporarily at the presenting primary and adjacent metastatic sites with exposure doses of from 8,00 to 10,000 r delivered in one hundred days. On the other hand, doses of the same magnitude did result in the initial resolution of the presenting cancers in 4 cases.

Exceptionally severe reactions appeared in 3 patients. One of these was a case of primary carcinoma of the posterior oropharynx in which edema of the entire oropharynx was prompt in onset and extreme in degree. This subsided partially but recurred some months later and simulated recurrence of cancer. The patient died of pharyngeal hemorrhage eight months after commencing treatment, and at autopsy no persistent or metastatic cancer was found. One patient with extensive cancer of the tongue and floor of the mouth had, at the end of treatment, actual gangrene of the anterior third of the tongue with microscopically persistent tumor in other portions of it. One case was complicated by the fact that there was persistent hard edema of the neck at the site which was subjected to the high dose radiation therapy after having previously been treated elsewhere with 2,000 to 3,000 r of medium voltage roentgen rays. In 2 patients the disease was controlled at the originally presenting sites but metastases have appeared elsewhere. In cases with cancer persistent at the originally presenting site at the end of treatment there was, of course, no way of knowing whether or not the tumor might have been destroyed if the dose had been greater. Our observations suggested that the limitation of tissue tolerance for the doses and treatment times described had been reached.

Various degrees of nutritional failure and constitutional exhaustion could be attributed, in part at least, to the radiation reactions which resulted in loss of appetite, loss of taste, and painful eating and swallowing. Persistent and painful radiation ulcers of the tongue were fairly characteristic in patients treated for oral or oropharyngeal cancer and these persisted for days or for weeks following the radiation therapy. Because of the severity of symptoms due to the intense radiation reactions, lateral pharyngostomy was performed in 3 patients and the operation was the immediate cause of death in at least 1 patient. This study has emphasized to us that lateral pharyngostomy probably should be done as an elective, preliminary procedure in patients with extensive oral or oropharyngeal cancer who are going to receive high dose, large volume radiation therapy. Where

this has been done succesfully, nutrition and general well-being have been much better maintained.

Superficial reactions of the skin have been of no consequence for they have not in any instance exceeded moderately deep tanning with, perhaps, a dry desquamation. Even in instances where tangential or overlapping irradiation or high dose transmitted irradiation occurred, as in the thin submental tissues, there was no greater reaction than deep tanning without blistering or ulceration. Within the time of observation of this clinical material, there have been no delayed necrotizing effects in the skin. What role, if any, the prolonged time of the irradiation played in these diminished skin reactions was not studied for it is difficult to meet the necessary experimental conditions due to the diminished surface and near-surface ionization at 2 mev. energy. It is considered that the distribution of the ionization is the critical factor in the diminished skin effects rather than the prolonged treatment time.

No complications due to irradiation were observed in the mandible or superior maxilla with 1 exception. This was a case of primary carcinoma of the nasopharynx in which a posterior molar had to be extracted soon after commencing treatment. Localized necrosis of the alveolus has appeared at the site of the extraction. Necrosis of bone did occur in the paranasal sinus cases, but in these instances it could be attributed to destruction by tumor.

Many of the patients had low grade, concurrent fevers and in those patients dying with cancer there were, of course, terminal cardiorespiratory complications of major importance. Constitutional deterioration of lesser or greater degree occurred in all of the patients and this seemed to be related in large part to problems of maintaining adequate nutrition. Two patients died of massive hemorrhage from the primary site of disease, 1 from pulmonary metastases, and the other deaths were from various pulmonary complications associated with uncontrolled primary or metastatic disease and severe radiation reactions. The intense reactions and prolonged hospitalization resulted in psychologic problems of considerable importance for depression was present to some degree in all patients and was severe in some. Various degrees of drug addiction occurred, but the duration of life was relatively so short that this became a problem in only 1 case.

DISCUSSION

It is the opinion of the authors that the limits of normal tissue tolerance in, at least, the oral cavity and the oropharynx have been reached or exceeded with a tumor exposure dose of 10,000 r given through a midline beam area of 90 cm.^{2} by either rotational or multiple, fixed field techniques in one hundred days. Garcia[8] has developed a mathematical concept of the tolerance dose to tissues in the female pelvis in respect to both volume and time conforming with the equation:

$$D_B = \frac{4{,}200}{r^{0.25}} (t^{0.25})$$

where D_B is the parametrial dose (in roentgens), 4,200 a proportionality or radiosensitivity constant, r a radius function given the numerical value of the radius of the circle of area equal to that of the cross section and interposed gap of the treatment fields, and t is the total treatment time in days. Garcia's results in the treatment of carcinoma of the uterine cervix became significantly impaired when the parametrial dose exceeded 105 per cent of the value indicated by this equation. Applying this same equation to an irradiated volume of the oropharynx with a midline beam area of 90 cm.^{2}, one would arrive at a limiting tolerance dose of 6,500 r in one hundred days. On the other hand, doses of 8,000 r given in eighty-five to one hundred days did seem to be tolerated where given through small fields (60 cm.^{2}) or to "nonsensitive" sites.

Solution of the cancerocidal dose equation:[1]

$$D = 2{,}750t^{0.23}$$

for the destruction of squamous cell carcinoma gives a value of 8,000 r for a treatment time (t) of one hundred days. It would seem, therefore, that the average cancerocidal dose and the tissue tolerance dose for large volumes of a variety of normal tissues treated for extended irradiation times are either similar or that the former exceed the latter.

The Baclesse[4] study of cases of carcinoma of the larynx showed a high correlation of the tumor dose and the time in which the dose was administered and it was inferred that prolongation of the treatment time, with appropriately increased doses, resulted in a diminution of the incidence of complications and deaths. This impression could not, however, be confirmed statistically for no significant maximal survival was found for either a given dose or time of treatment. In the dose range from 3,000 to 9,000 r of 200 kv. peak roentgen rays and a corresponding range in time from seventeen to one hundred and ten days there was no significant difference in mortality. Baclesse inferred that equally good results were attained by prolonging the time of treatment with appropriately increased doses without attendant severe mucosal and other normal tissue reactions. This, again, was not confirmed statistically. Similarly, Garcia has concluded that there are no differential tissue effects related to prolongation of treatment time, *per se*.

If differential tissue effects do indeed appear as the result of prolongation of the irradiation time it would seem on the basis of the Garcia, Baclesse and other data and the present study that these differential effects must be very subtle and perhaps not of a degree to be clinically significant. On the other hand it is a well known phenomenon that gross differences in the radiosensitivities of cells and tissues do exist but it would appear that these very gross differences are not related to the time of irradiation. In a highly varied population of cells, such as would obtain among the various tissue types in the treatment of human malignant neoplasms and when the irradiation of adjacent or supporting normal tissues is concerned, it would be expected that average cell division times will vary from tissue to tissue but that the division of any particular cell would be a random event. Over the course of a very prolonged irradiation time, these random events would average out so that only gross dose differences, but not differential tissue effects due to time of the irradiation, would be observed. This is a theoretic aspect of the applied radiation problem which might very well be subjected to the experimental approach, using the tissue culture technique for the propagation of clonal strains of mammalian cells as described by Puck[12] and in induced synchronous cell division as described by Mazia.[10]

SUMMARY

A limited but systematic study of the dose and time and, to a lesser degree, of the volume relationships for the radiation treatment of cases of extensive cancer of the sinuses, mouth and oropharynx over periods of time ranging from eighty to one hundred days and with tumor exposure doses of 8,000 to 10,000 r has been reported.

It would appear that extension of the conventional dose-time plot is valid in indicating, at least, an appropriate or optimal tumor dose and in establishing the limits of tolerance for large tissue volumes irradiated under these conditions.

Limiting skin effects were not observed for the irradiation technical factors and for the doses and treatment times employed.

Differential neoplastic and normal tissue effects were not observed which could be accounted for by prolonged extension of the treatment time. Both the neoplastic and normal tissue responses were similar to what might be expected from lower doses given in a shorter period of time.

The limits of tissue and patient tolerance are reached or exceeded when an exposure dose of 10,000 r more or less homogeneously distributed throughout a large volume of

the oral and oropharyngeal tissues is given in one hundred days.

Doses of this order of magnitude are not necessarily cancerocidal. Further improvement in the results of the radiation therapy of these types of cases may have to be sought in pharmacologic modifiers of response in neoplastic and normal tissues.

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CONTINUOUS VISUAL MONITORING OF 2 MEV. ROENTGEN THERAPY*

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THE attainment of a high efficiency factor, that is, a high ratio of absorbed dose in tumor to absorbed dose in the organism or in its normal organs and tissues, is the principal technologic consideration in cancer radiation therapy.[1] Attainment of a high efficiency factor in external irradiation is dependent upon the selection of the appropriate ionizing particles or photon radiation, the pattern of the radiation distribution, and the precise orientation of the beam to the tumor and the patient so that the most effective pattern of radiation can be realized. There are several ways of achieving this last. The simplest and generally most useful way of relating internal structures and tumors to the general anatomy of the patient is by external anatomic landmarks. Experience with roentgenographic and continuous fluoroscopic visual monitoring of patients undergoing radiation therapy has shown that, while simple, this method may be also be highly inaccurate. A greater degree of accuracy can be attained by fluoroscoping the patient prior to treatment and making external marks by means of which internal structures may later be oriented to the beam. Experience with this method has shown that there are many inherent inaccuracies since the orientation of the patient may not be the same under conditions of treatment as under the conditions of exploratory fluoroscopy. The procedure is also time-consuming, requiring not only the exploratory and marking operation itself, but time for dark adaptation. This method, in essence, is simply a refinement of identification by reference to external landmarks. A pre-treatment and post-treatment roentgenogram is useful since it provides a permanent record of beam orientation and field size. If changes in beam orientation occur during treatment these are not, however, instantaneously recognized and corrections can be made only subsequent to the actual treatment. This is a highly impractical method to use on a day to day basis or even intermittently as it is also very time-consuming, although it constitutes an improvement over dependence upon external anatomic or other landmarks alone. Continuous fluoroscopic monitoring of beam orientation, if accomplished simply, would obviously permit the most precise means of control for it is instantaneous. By the introduction of appropriate controls at the monitoring site, simultaneous changes in or corrections of slight errors of beam orientation can be effected. It is this latter method and its application in 2 mev. roentgen therapy which will be described. The methods discussed are summarized in Table 1.

The interaction of high energy photon beams with known fluorescent material does not result in sufficient energy conversion to illuminate the fluorescent screen to a degree adequate to be picked up by the industrial type image tube and television circuitry. The introduction of a high amplification factor and contrast circuitry is essential to the securing of a useful picture at the control station. The Johns Hopkins[2] screen intensifier as developed by the Friez Instrument Division of the Bendix Aviation Corporation* provides such amplification and contrast factors in commercially avail-

* The Bendix-Friez "Lumicon," Friez Instrument Division, Bendix Aviation Corporation, 1400 Taylor Avenue, Baltimore 4, Maryland.

* From material exhibited at the Forty-second Annual Meeting of the Radiological Society of North America, Chicago, December 2–7, 1956.

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TABLE I

MONITORING METHODS

Method	Advantage	Disadvantage
External anatomic landmarks, pointers, and back-pointers	Simple	Inaccurate
Roentgenographic	Permanent record	Time consuming, cannot be performed simultaneously with the irradiation
Continuous fluoroscopic	Accurate, simple, can be performed simultaneously with the irradiation	Requires elaborate instrumentation

able equipment well adapted to use for continuous visual monitoring of high energy photon beams. The instruments are illustrated in Figures 1 and 2, the fluorescent screen and orthicon and signal amplifier circuits being contained in the box-like structure in Figure 1 and the final amplifier, control circuits and kinescope being shown in Figure 2. The image pickup system shown in Figure 1 can be raised or lowered on the vertical column to any required level. A schematic diagram of the transmission system is shown in Figure 3.

In practice, the following procedure, or a minor modification of it as may be appropriate to the particular problem, is employed in setting up the patient. The procedure begins in the target area with the fixation of the patient in the rotating chair, the identification of external landmarks, and finally the tentative orientation of the patient and the roentgen ray beam. One has, of course, determined from previous clinical studies and the conventional or special roentgen examinations just what part is to be treated and the beam size

FIG. 1. The target room. From left to right: the collimating device of the 2 mev. Van de Graaff accelerator, the patient in the rotating chair, and the fluorescent screen, orthicon, and signal amplifier.

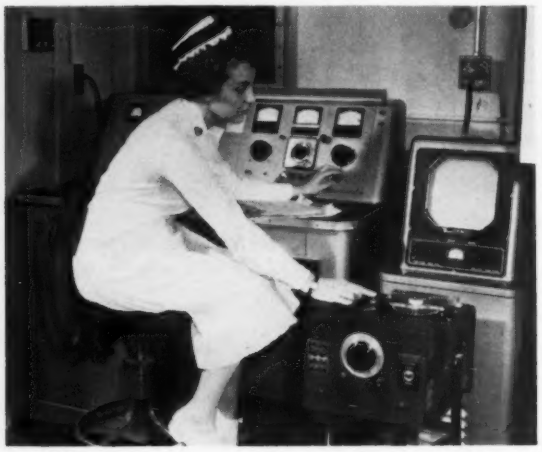

FIG. 2. The control room. Left, control console of 2 mev. Van de Graaff accelerator. Right, kinescope, final amplifier, and control circuits. Below, rotating chair controls. The roentgen-ray generator may be raised or lowered in the vertical axis from the control console and the chair may be moved about the two horizontal axes from its external control.

which is to be employed. The procedure is continued as shown in Table II.

While the procedure appears complicated in operation, it actually is effected quite easily. Once the required orientation of the beam, patient and tumor has been secured by direct visual inspection, external marks can be placed with a degree of accuracy not possible by other methods and these will serve as tentative check points for the next treatment. After a short experience has been gained with the method, it has been found that subsequent corrections will be minor and can be effected while the patient actually is rotating. Experience has also shown that the dose received by the patient in rotational techniques where, however, the chair may be stationary for a few moments for checking purposes, will be less than 5 per cent of the total dose to the tumor. For this reason, the additional dose is not accounted for separately in determining dose and distribution. The method is equally applicable to fixed field techniques.

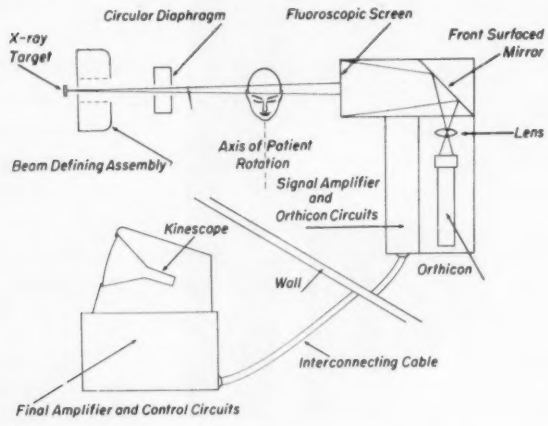

FIG. 3. Schematic diagram of roentgen-ray beam and beam image transmission system.

TABLE II

PROCEDURE OF MONITORING

In the target area:
1. Fixation of patient in rotating chair
2. Identification of external anatomic landmarks
3. Tentative orientation of patient and beam

In the control area:
1. Starting of generator and switching on beam
2. Inspection of image of transmitted beam in one axis and adjustment of beam alignment by appropriate manipulation of external controls for: (a) rotating chair position-shifting mechanism, (b) vertical positioning of beam
3. Stopping of generator and rotation of chair to 90° axis
4. Starting of generator and switching on beam
5. Final adjustment in 90° axis as in No. 2, above
6. Commence rotation

Conventional contrast media are not utilized because their density is not sufficiently different from that of soft tissue to allow a clear distinction at this high energy of radiation. The only effective contrast media are either very low or very high density materials such as air and mercury, respectively. Figure 4 demonstrates this characteristic on a roentgenogram made with the 2 mev. Van de Graaff generator of a variety of contrast media, including air and mercury, set in a masonite block. Where the dimensions of the column are very small, as in a narrow esophageal tube, mercury must be used to supply sufficient contrast. Mercury is also useful in the lumen of a Foley catheter for identifying the bladder base. Air contrast will ordinarily provide sufficient distinction to en-

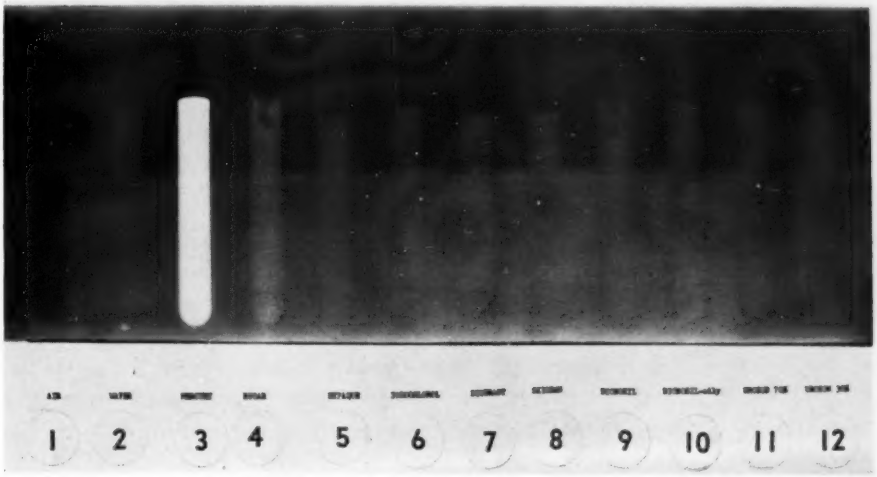

FIG. 4. A 2 mev. Van de Graaff roentgenogram of a variety of contrast media in test tubes in a pressdwood block. From left to right: (1) air; (2) water; (3) mercury; (4) rugar; (5) hypaque; (6) iodochloral; (7) diodrast; (8) skiodan; (9) dionosil; (10) dionosil, oily; (11) urokon, 70 per cent; (12) urokon, 30 per cent. Of the group, only air and mercury are satisfactory contrast media.

able the sphenoidal sinus and pituitary fossa to be recognized and to allow for adequate visualization of the nasal, oral, pharyngeal, and laryngeal passages. The bladder may be inflated with air and the vagina may be distended with a large plastic test tube or the air containing shell of a Victoreen ionization chamber. The trachea and main bronchi can be clearly distinguished as well as the lung fields. The domes of the diaphragm can be distinguished from the lung fields and the cervicodorsal spine ordinarily can be seen. There is sufficient contrast between non-air containing hilar and pulmonary lesions and adjacent lungs to allow their visualization. In other words, tissue contrast differentiation is either generally sufficient or there are means of introducing catheters of radiopaque media into hollow organs so that most of the tumors or tumor sites requiring a high degree of precision in beam orientation can be visualized and kept under continual visual monitoring. An actual photograph of a "Lumicon" screen image is shown in Figure 5 where the esophagus is visualized by a column of mercury in a tube, and the posterior cardiac border and dome of the diaphragm are shown by contrast with the air containing lung.

FIG. 5. Photograph of kinescope image showing mercury-filled tube in esophagus, edge of spine, retrocardiac space, heart and diaphragm.

CONCLUSION

A system for the continuous visual monitoring of 2 mev. roentgen therapy has been described. The use of this system has intro-

duced a degree of precision in securing and maintaining beam orientation not attainable by the use of other methods.

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EFFECTS OF RADIATION ON METASTATIC LYMPH NODES FROM VARIOUS PRIMARY CARCINOMAS*

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THE question has often been raised whether it is possible to sterilize carcinomatous lymph nodes with irradiation.

While many radiotherapists are certain that beneficial results can be secured by treating metastatic lymph nodes with high dosages, a large number of surgeons, gynecologists and even radiotherapists does not approach with enthusiasm the idea of treating such lymph nodes. In the belief that it is impossible to achieve lasting results, this group uses only small dosages for temporary growth restraint and does not realize that the predictable failure of such a method will only render disservice to radiation therapy.

I have always felt very strongly in the affirmative way; namely, that it is possible to sterilize lymph nodes in patients having lymph node metastases. It was for this reason that I have repeatedly emphasized the need for postoperative irradiation of lymph node bearing areas after surgery, especially when the pathologic specimen had shown a large number of positive lymph nodes.

It is difficult to prove the accuracy of such clinical observations since it requires histologic examinations of lymph nodes before and after radiation therapy. However, the recent awareness of the importance of recognizing the sometimes unexpected spread of even small carcinomas to distant lymph nodes and the dependency of the prognosis on the involvement of such lymph nodes has led to more frequent lymph node biopsies before a decision as to the type of therapy is made.

In this study, the postradiation material for the microscopic examination was obtained from subsequent lymph node dissections and autopsies. The lymph nodes of interest were: (1) The neck lymph nodes in primary carcinoma of the head and neck, and the axillary lymph nodes in a primary carcinoma of the palm of the hand; (2) the pelvic lymph nodes in primary carcinoma of the cervix which were removed some months after radiation therapy; and (3) the internal mammary and axillary lymph nodes which were biopsied at the Francis Delafield Hospital, New York City, before a radical mastectomy was to be decided upon, and which were only treated with external irradiation when found to be positive.

Table 1 shows that only a small group lends itself to microscopic comparison before and after radiation therapy in spite of a relatively large number of patients with lymph node biopsies.

All patients were treated with an iden-

TABLE I

Total Number of Patients with Proved Positive Lymph Nodes before Treatment			62
Squamous Cell Carcinoma		**Adenocarcinoma**	
head and neck	10	breast	50
hand	1		
cervix	1		
	12		50
Microscopic Examination of Lymph Nodes before and after Therapy			23
head and neck	10	breast	11
hand	1		
cervix	1		
	12		11

* From the Francis Delafield Hospital, Columbia University College of Physicians and Surgeons, New York, New York. Presented at the Thirty-ninth Annual Meeting of the American Radium Society, Quebec City, Quebec, Canada, May 29–June 1, 1957.

This work was supported in part by a grant from the National Cancer Institute of the National Institutes of Health, Public Health Service.

TABLE II

SQUAMOUS CELL CARCINOMA

No. of Patients	Location	Size of Lymph Nodes at Beginning of Therapy	Status after Therapy	
			Lymph Nodes	Primary Tumor
1	nasopharynx	3 cm.	neg.	neg.
1	nasopharynx	5 cm.	pos.	neg.
1	nasopharynx	3 cm.	neg.	neg.
1	base of tongue	"large"	pos.	neg.
1	base of tongue	2 cm.	neg.	neg.
1	base of tongue	2.5 cm.	neg.	pos.
1	epiglottis and larynx	5 cm.	pos.	pos.
1	epiglottis and larynx	small	neg.	neg.
1	floor of mouth	6 cm.	pos.	neg.
1	post. pharyng. wall	2–3 cm.	neg.	pos.
1	palm of hand	"diffuse infiltrating"	neg.	surgical removal

tical tumor dose of 5,000 r delivered in five weeks, with either the 2 mv. or the cobalt 60 unit. Lymph nodes and primary lesions were treated in the same fashion.

I—SQUAMOUS CELL CARCINOMA

Table II brings out two pertinent points which we encountered repeatedly in various lymph node bearing areas in the course of these studies: (1) The size of the lymph nodes had a definite influence on the outcome of the therapy inasmuch as larger lymph nodes respond less favorably than smaller ones. (2) Metastatic lymph nodes may become and remain free of disease after treatment while an extensive primary lesion continues to show active carcinoma.

The case of the patient with squamous cell carcinoma of the palm of the hand is of particular interest. This patient's disease had developed after radiation damage and he was treated surgically with amputation of the hand and forearm. Five months later a radical axillary dissection for axillary metastases was attempted, but some disease was left behind when it was found that "the large vessels were too closely involved." Radiation therapy to the axilla was then given. Three years after completion of therapy this patient died of a coronary occlusion, and on autopsy no evidence of carcinoma was found.

TABLE III

CARCINOMA OF CERVIX

Stage	No. of Patients	No. of Patients with Negative Lymph Nodes after Radiation Therapy
I	10	10
II	10	9
III	5	4
Total Cases	25	23

In the group of patients with squamous cell carcinoma of the cervix, only 1 patient had microscopic examinations before and after radiation therapy. This patient's scheduled operation was abandoned when multiple biopsies of different lymph nodes proved positive. The patient was treated on the 2 mv. unit with a tumor dose of 5,000 r throughout the pelvis and in addition with radium applied in Manchester ovoids for a dose of 5,000 r to Point A. Six months after therapy the primary disease appeared to be controlled and a lymph node dissection was carried out. All lymph nodes were negative. The patient is alive and well five years after completion of therapy. The findings in 24 other patients who had lymph node dissections only AFTER radiation therapy can be evaluated only by comparison with statistics of patients who have had lymph node dissections without previous radiation therapy (Table III).

TABLE IV

NO. OF PATIENTS WITH POSITIVE LYMPH NODES IN CARCINOMA OF THE CERVIX

	To Be Expected	Our Material
Stage I	17 out of 100	0 out of 10
Stage II	31 out of 100	1 out of 10
Stage III	66 out of 100	1 out of 5

TABLE V

ADENOCARCINOMA OF THE BREAST

No. of Patients with Positive Axillary Lymph Nodes before Beginning of Radiation Therapy	Size of Lymph Nodes at Beginning of Radiation Therapy	No. of Patients with Negative Lymph Nodes after Radiation Therapy
10	Between 3 and 5 cm., often fixed	4
No. of Patients with Positive Internal Mammary Lymph Nodes before Beginning of Radiation Therapy	**Size of Lymph Nodes at Beginning of Radiation Therapy**	**No. of Patients with Negative Lymph Nodes after Radiation Therapy**
11	Often "completely replaced by tumor" but not larger than 1 cm.	7

The figures which are given in the literature for incidence of positive lymph nodes in carcinoma of the cervix are: Stage I, 17 per cent; Stage II, 31 per cent; Stage III, 66 per cent. Although our figures are small and a statistical evaluation might seem to be somewhat forced, I think it is interesting and instructive to compare them with the forementioned figures as shown in Table IV.

Each of the 2 patients with positive lymph nodes had only one large diseased lymph node; other lymph nodes were found to be negative. The primary disease had been controlled in all but 1 patient.

II—ADENOCARCINOMA

There were 11 patients with adenocarcinoma of the breast in whom we were able to observe the response to radiation therapy in 2 lymph node bearing areas, the axillary and the internal mammary area. The primary lesions in 10 of these patients were clinically described as inoperable, and all these patients showed residual disease in the primary area after radiation therapy. The eleventh patient was free of disease after irradiation. Table V shows that in several patients the axillary and internal mammary lymph nodes became negative after radiation therapy while the active disease in the primary lesion persisted and seemingly there appeared to be no response of the large lymph nodes.

Not included in Table V are 22 patients who are still alive and have had no postradiation lymph node biopsies. All 22 patients had positive triple biopsies and were found to be unsuitable for surgery; therefore they received only radiation therapy to primary and secondary lesions. None has had any evidence of disease three to five years after completion of radiation therapy.

SUMMARY

This is a preliminary report. The material is too small to arrive at far-reaching conclusions; however, the following four observations repeated themselves frequently enough to form the basis for future study:

1. There seemed to be no difference in the response to irradiation between metastatic squamous cell carcinoma and adenocarcinoma.
2. There was no difference in the response of lymph nodes in different areas.
3. Smaller lymph nodes responded better than large ones.
4. Metastatic lymph nodes could be sterilized by irradiation while there was still persistent disease present in the primary area.

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Vol. 79, No. 1

THE TOXICITY IN MAN OF HEXAVALENT URANIUM FOLLOWING INTRAVENOUS ADMINISTRATION*

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THIS investigation was undertaken for the dual purpose of deriving an intravenous tolerance dose of hexavalent uranium for man and the procurement of data pertinent to the distribution and excretion of this ion in man to aid in evaluating exposures in uranium processing and fabrication plants. The findings relative to this latter purpose have been described in a previous publication.[8]

The determination of an intravenous tolerance dose is an initial step in evaluating the possible application of U^{235} to the neutron capture therapy of brain tumors. The recent studies of Javid, Brownell and Sweet,[4] and Sweet and Javid[9] pointed out the possible use of the neutron capturing isotope boron 10 for the radiation therapy of these tumors, and the more recent publications of Farr *et al.*,[1] and Godwin *et al.*[2] have described the initial results in a group of 10 patients with glioblastoma multiforme treated with this isotope. The theoretic possibilities of using lithium 6 as the neutron capturing isotope have been explored by Luessenhop, Sweet and Robinson.[4]

The rationale of this form of therapy stems from several well established physiologic observations. The normal operation of the "blood-brain barrier" tends to limit the passage of certain substances into the extracellular space of the brain. In glioblastoma multiforme, one of the most malignant forms of brain tumor, the barrier phenomenon is much less pronounced in that a more rapid exchange of a substance between the blood and extracellular space of the tumor occurs than between the same compartments in the normal surrounding brain. Accordingly, the intravenous administration of a neutron capturing isotope leads to its greater concentration in the brain tumor, and because this isotope becomes the chief determinant of the evolved radiation energy following exposure to a flux of thermal neutrons, it presents the possibility of selectively destroying the tumor without significantly damaging the normal brain.

In the quest for isotopes that might be employed in this scheme, the use of certain fissionable isotopes was suggested. Following careful theoretic evaluation of the clinical use of U^{235}, it was concluded that its possibilities in neutron capture therapy were worthy of investigation. Although the capture cross section of U^{235} for thermal neutrons is substantially less than that of boron 10 and lithium 6, the fission energy following capture is considerably greater. In addition, the tremendous size of the uranium atom suggests a more complete exclusion by the blood-brain barrier and hence a more efficacious differential concentration between tumor and normal brain.

The preliminary steps necessary, before the therapeutic possibilities of this isotope can be evaluated, consist of: (1) finding a tolerance dose for man, and (2) determining the differential concentration of uranium in normal brain and brain tumor and the time interval over which it persists.

Prior to this study there were considerable data concerning the toxicity of urani-

* This study was supported by grant No. AT(30-1)-1093 from the United States Atomic Energy Commission.
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TABLE I

Patient	Age	Sex	Weight	Uranium Injected	Mg. U/kg.	Duration of Life After Injection
I	26	M	55.9 kg.	5.5 mg.	0.097	2.4 days
II	47	M	57.4	5.9	0.13	60
III	34	M	60.0	4.3	0.07	566
IV	63	F	67.7	11.2	0.17	42
V	39	M	55.9	15.8	0.28	63

um in animals.[11] This information revealed a considerable species difference in tolerance to intravenously administered hexavalent uranium; *e.g.*, mice tolerated 100 times more than rabbits, and certain strains of mice, 200 times more. Thus there was no clue to man's tolerance, but the data furnished valuable information concerning the distribution and mechanism of toxicity and suggested laboratory methods by which the initial signs of toxicity in man might be discerned.

METHODS

Selection and Care of Patients. The important information concerning the 5 patients included in this study is shown in Table I. In all cases the diagnosis of glioblastoma multiforme or of astrocytoma of the dominant hemisphere had been established by a craniotomy. At the time of injection all but Patient I were in generally good physical condition and all were without definite evidence of pathologic processes other than their cerebral disease. With the exception of Patient III, who lived for seventeen months following injection, all were in coma or semicoma and remained so until their demise. They received the usual hospital care for comatose patients, consisting of indwelling catheters, feeding by gastric tube when necessary, frequent turning, antibiotics and tracheal suction when necessary. The gastric feeding was given every two hours and the volume of each feeding adjusted to prevent too great a gastric residuum. At times it was necessary to augment the tube feedings with intravenous fluids. Patients II and III were taking some oral feedings during the time of injection.

Preparation of Injection Solution. Pure uranium oxide (U_3O_8) was converted to nitrate ($UO_2(NO_3)_2$) by dissolving the oxide in an excess of nitric acid and evaporating to dryness. The resulting nitrate crystals were dissolved in distilled water and repeatedly evaporated to dryness to eliminate final traces of nitric acid. The crystals were then dissolved and diluted to volume with distilled water. The solution was assayed colorimetrically and by alpha counting. The desired quantity of the nitrate was placed in a rubber sealed container and autoclaved for sterility. A sterile 0.4M sodium acetate solution was mixed with the nitrate solution in equal volumes shortly before injection to adjust the pH to 5.5 to 6.0.

Injection Procedure. In all patients the uranium solution was injected into an antecubital vein over a period of ten to fifteen seconds. To preclude the possibility of extravasation, a continuous intravenous injection of normal saline was started and observed for subcutaneous leakage. The uranyl nitrate solution was taken up in a graduated syringe and injected into the intravenous tubing. With the first patient a metal threeway stopcock was used, but this resulted in the loss of a small but significant amount of solution by leakage. In the second patient a glass threeway stopcock was employed, but near the end of the injection the glass arm broke and again a small amount of the solution was lost. The remainder of the injections were made by inserting a No. 22 needle on the syringe

directly into the lumen of the rubber intravenous tubing. The syringe was irrigated four or five times with saline from the intravenous bottle prior to its removal from the tubing.

Following the injection, the syringe employed in the administration was used to deliver replicate volumes of the injection solution to several flasks for determination of uranium content. This afforded an accurate check on the amount of uranium injected.

Collection of Specimens. The methods of collection and analysis of blood, urine, feces and bone specimens for uranium content have been described in a previous publication.[8]

Urine specimens, collected from indwelling catheters, were taken at hourly intervals during the first twenty-four hours and thereafter at twelve hour intervals for pH, specific gravity, volume and uranium content. Specimens for glucose, acetone, albumin, catalase, and microscopic examination were taken directly from the catheters. For calculation of clearances, samples of the urine collections were taken for creatinine, urea, and chloride determinations.

Blood specimens for hematologic tests, uranium content, liver function tests, electrolytes, total protein, nonprotein nitrogen and amylase were drawn by phlebotomy at varying intervals both before and after injection. Blood samples for urea chloride and creatinine were drawn at twenty-four hour intervals. Intravenous glucose tolerance tests were performed on 3 of the patients.

Analytical Methods. The presence of glucose in the urine was determined by Benedict's qualitative test and, if present, subjected to Benedict's quantitative test. The nitroprusside test was used to detect acetone bodies. The sulphosalicylic acid method of Kingsbury, Clark, Williams and Post (*J. Lab. & Clin. Med.*, 1926, *11*, 981) was employed for the quantitative determination of urinary protein. For microscopic urinalysis, 15 ml. of fresh urine was centrifuged at 2,000 rev./min. for five minutes and the supernatant discarded. The BSP test was performed by injecting 5 mg. of bromsulphalein per kilogram body weight and procuring a blood sample forty-five minutes later, as described by Mateer, Baltz, Marion, and Macmillan (*J.A.M.A.*, 1953, *121*, 723).

Urinary catalase was determined by a manometric method employing the Warburg apparatus as described by Wills (Voegtlin and Hodge: Pharmacology and Toxicology of Uranium Compounds, McGraw-Hill, 1949, p. 270). In the cases where urinary content of catalase was sufficiently high to approach the limitation of maximum reading on the manometers, separate determinations were made on samples of urine diluted 1:5 and 1:20. This procedure consistently resulted in significantly higher values. The final results of each determination were recorded as cc. C_2/0.2 ml. of urine.

The remainder of the analyses were performed by the clinical laboratory of the Massachusetts General Hospital by methods described in the *New England J. Med.*, 1950, *243*, 748.

RESULTS

Clinical State. The parlous clinical state of the patients made interpretation of the vital signs difficult. In general, there were no consistent or marked changes in blood pressure, pulse, respiration, or body temperature that could be attributed to the uranium injection. There were no obvious dermal changes such as erythema, sweating, or eruptions. No change in gastric residua or stools was noted. The neurologic status of the patients remained unaltered.

Cardiac Status. Electrocardiograms were performed on all the patients preceding and one to three days following the uranium injection. No changes from the control readings were noted, with the exception of Patient IV. This patient had a sinus tachycardia for three days preceding the injection, and ten hours following the injec-

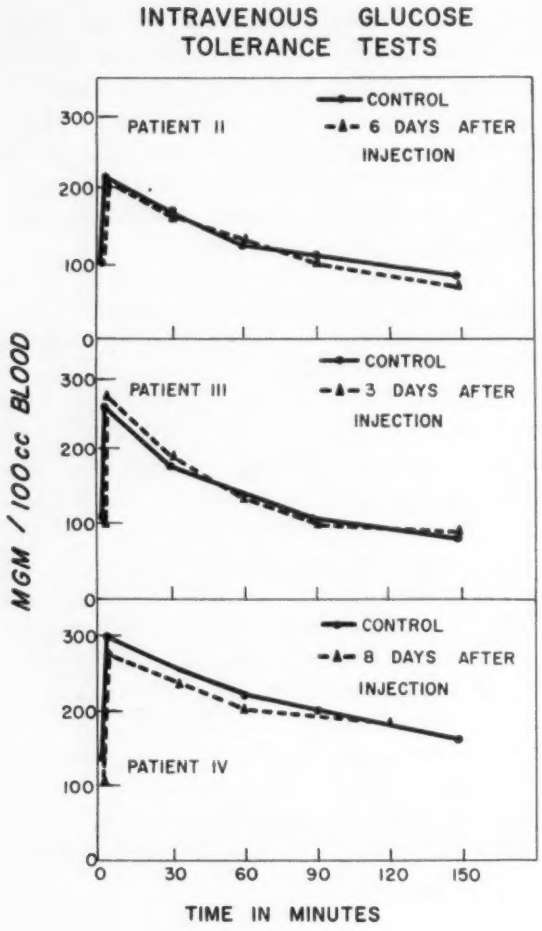

FIG. 1

tion began to have extrasystoles. The electrocardiographic tracing on the second day following injection was interpreted as showing a sinus tachycardia with occasional ventricular premature beat. The extrasystoles disappeared on the fifth day, but the tachycardia persisted for the remaining twenty-seven days of hospitalization.

Glucose Tolerance Tests. The preinjection and postinjection intravenous glucose tolerance tests, which were performed on Patients II, III, and IV, are shown in Figure 1. In all 3 patients the preinjection and postinjection curves closely coincide.

Liver Function Tests. The results pertinent to hepatic function are shown in Table II. Patient I showed definite evidence of hepatic damage both before and following the injection. To a large measure, this

TABLE II

Patient	I			II			III			IV					V				
Day After Injection	Control	1	2	Cont.	1	6	Cont.	1	5	Cont.	2	8	22	29	Cont.	2	6	19	26
BSP, % Retention 45 min.	32%		36%	8%		8%			0%	12%		12%			8%				
Cephalin (24 hours	3+	2+		±	2+	0	2+	2+	1+	0	0	0	0	0	0	0	0	0	0
Flocculation (48 hours	3+	3+		1+	3+	2+	2+	3+	2+	0	1+	0	0	0	1+	1+	0	0	0
Thymol Flocculation				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Thymol Turbidity		8.5		2.4	1.5	2.5	3.5	2.6	3.0	3.5	2.5	2.5	3.0	2.0	1.0	1.5	1.5	3.0	2.0
Cholesterol, mg.%	288	194		224	208	234	249	237	218	248	251	237	249	291	232	245	240	250	250
Cholesterol Esters, mg.%	149	153		215	125	135	160	147	141	126	161	154	167	175	119	114	130	163	174
Serum Bilirubin, mg.%	0.6	4.4		0.3	0.3	0.5	0.3	0.3	0.2	0.5	0.5	0.2	0.2	0.3	0.4	0.2	0.2	0.2	0.3
Prothrombin Time, % of Normal	75%		55%	100%	100%	100%	100%	100%	100%			100%	70%		60%	60%	60%	50%	
												(day 14)				(day 1)		(day 12)	
Serum Albumin, gm.%	2.7	2.7	2.7	3.3	3.2	3.0	3.8	4.0	3.3	2.8	2.8	3.2		3.7	3.3	3.3		3.2	3.5

TABLE III

MICROSCOPIC URINALYSIS

Patient	I			II						III			
Day	−1	1	2	−2	2	4	7	10	23	−3	1	3	6
WBC./HPF.	8–12	10–15	1–2	15–20	8–10	4–6	Loaded	20–30	10–15	Occ.	Occ.	15–20	Many
RBC./HPF.	1– 2	1– 2	Occ.	10–15	Rare	10–12	Occ.	1– 2	0	0	0	4– 8	Occ.
Epi. Cells	Occ.	Occ.	0	0	0	0	0	0	0	0	0	0	0
Crystals	0	0	Amph. Phos.	Ca Ox.	Amph. Phos.	Amph. Phos.	Triple Phos.	Triple Phos.	Triple Phos.	0	0	0	Triple Phos.
Casts				0	0	0	0	0	0	0	0	0	0
Hyaline	Occ.												
Gran.	Occ.		Occ.										
Cells		Occ.	Occ.										

may be accounted for by the fact that his blood pressure was at shock levels during and preceding the time the testing was performed. Patients II and III each had an elevation of cephalin flocculation above the normal range on the first postinjection day, but this returned to normal and the other tests remained within the normal range. Patients IV and V failed to show any changes consistent with hepatocellular damage.

Hematologic Studies. Patients I and V had elevated leukocyte counts during the preinjection period, and the counts were not appreciably altered following injection. All the patients with the exception of Patient II had an increased number of polymorphonuclear cells on differential smear which remained unchanged during the postinjection period. No changes in the morphologic characteristics of the leukocytes were observed.

A drop in the hemoglobin was observed in all the patients. However, this was consistent with blood loss of 300 to 400 cc. necessary for the numerous chemical tests and blood uranium determinations.

As anticipated, the sedimentation rate was markedly elevated prior to injection. Patients IV and V had some increase in sedimentation rate, but this was consistent with the fall in hematocrit. Reticulocyte counts on Patients II and III showed no important changes. Since there were no changes in the apparent abundance of platelets on the blood smear, actual counts were not carried out.

Microscopic Urinalysis. The results of these studies are shown in Tables III and IV. The presence of abnormal numbers of

TABLE IV

MICROSCOPIC URINALYSIS

Patient	IV							V						
Day	−1	2	3	4	7	9	12	−2	1	2	3	6	9	12
WBC./HPF.	Occ.	40–50	20–30	10–20	Many	8–10	10–15	4–6	10–15	10–15	5–8	Many	4–6	1–2
RBC./HPF.	0	3– 5	10–20	Occ.	Occ.	0	10–15	0	Rare	1– 2	Rare	Occ.	0	0
Epi. Cells	0	Occ. Squam.	0	0	0	0	0	Few	0	0	0	0	0	0
Crystals	0	0	Urate	0	0	0	0	0	0	Urate	Urate	0	0	Triple Amph. Phos.
Casts	0	0	0				0	0						0
Hyaline									Occ.					
Gran.				Rare Coarse	Many Coarse and Fine	Occ. Fine				Many Coarse	Occ. Fine	Occ. Fine	Rare Fine	
Cells									Occ.	Many				

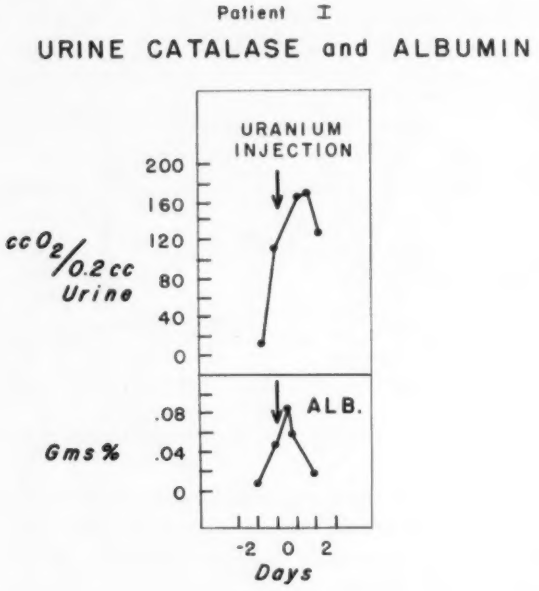

FIG. 2

leukocytes and erythrocytes was consistent with the indwelling catheters. Patient I had casts in his urine both before and after injection without change in abundance. Patients IV and V had casts only during the postinjection period. With Patient IV they made their appearance on the fourth day as a rare coarsely granular cast/high power field. On the seventh day the number of coarsely granular casts was greatly increased, and in addition there were many finely granular casts. On the ninth day, only an occasional finely granular cast/HPF was noted, and on the twelfth day none could be found.

Patient V had occasional hyaline and cellular casts/HPF on the first day, which changed to many coarsely granular and cellular casts/HPF on the second day. On the third, sixth, and ninth days, only a rare finely granular cast/HPF could be found, and on the twelfth day there were none.

Urinary Catalase and Protein. The results of the urinary catalase and protein determinations are depicted in Figures 2 to 6. The rapid demise of Patient I permitted too few determinations for proper evaluation. Patient III, who received the smallest dose, showed a temporary rise in

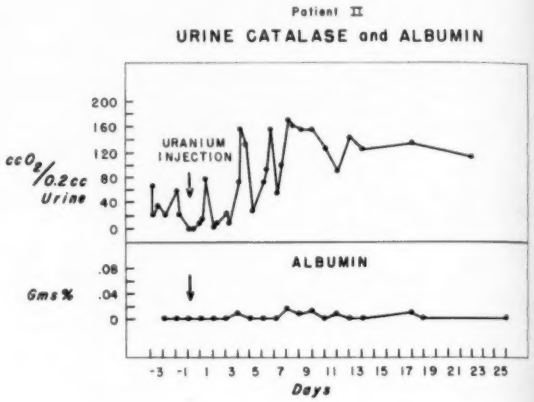

FIG. 3

catalase level on the first postinjection day, but this did not exceed a control determination three days prior to injection. Also this patient had a marked elevation in urinary protein on the day preceding injection which returned to normal during the first two days following injection. This obscured any slight effect of the uranium injection.

Patients II, IV and V, who received the largest doses, showed striking changes from the control values. In all 3 patients there was a tendency for double peaking of the catalase and protein elevations. The initial peak appeared during the second to fourth day and the second peak during the sixth to eighth day. There

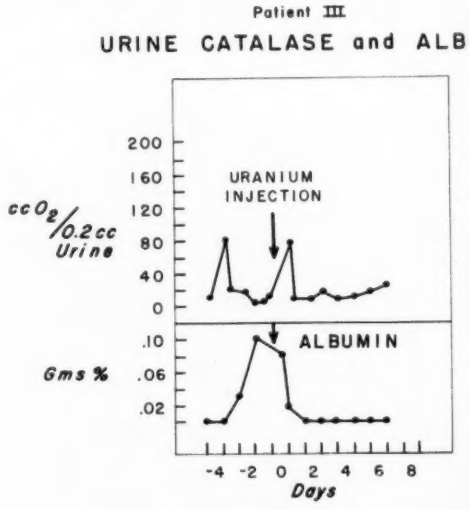

FIG. 4

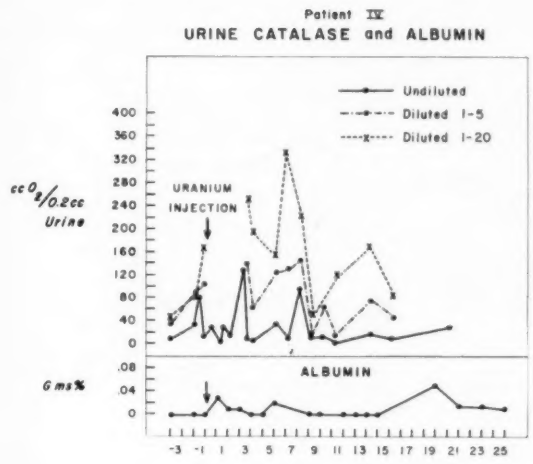

FIG. 5

appeared to be a tendency for the peaks to develop earlier as the dosage was increased. The greater catalase values obtained by diluting the urine sample tested are clearly apparent in the figures for Patients IV and V.

Renal Function Studies. The parameters employed to test renal function are shown graphically in Figures 7 to 10. The bar graphs at the bottom of each of these figures indicate the total twenty-four hour fluid intake and output. The possible

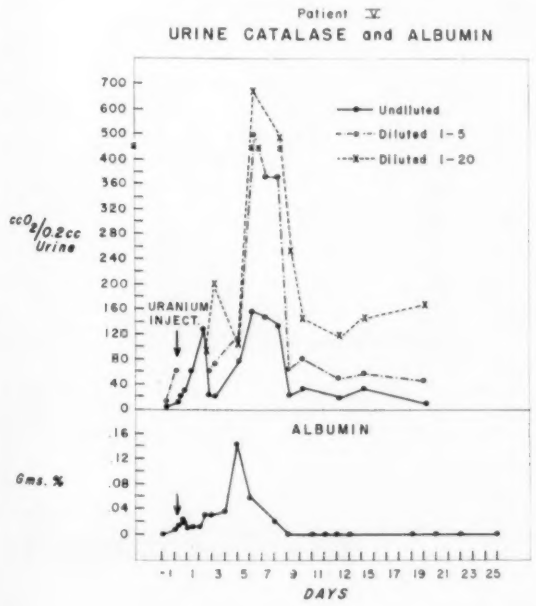

FIG. 6

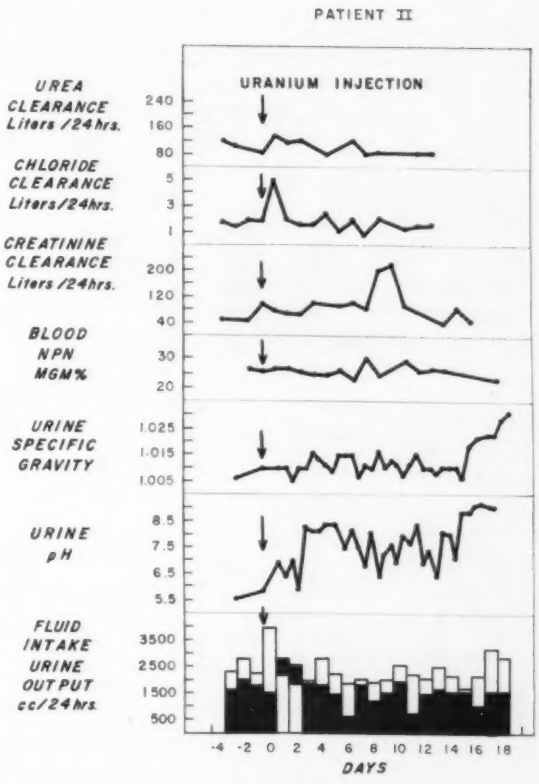

FIG. 7

effects of the uranium injection on the hourly urine output, specific gravity, and pH during the first twenty-four hours are shown in Figures 11 to 15. Prior to the uranium injection, the patients were in an adequate state of hydration as adjudged by control fluid balances and electrolytes.

Patient I failed to show a definite effect from the injection. The control output of 100 cc. of urine per hour fell to 20 cc. per hour by three hours following injection and remained at approximately this level for the next seventeen hours in spite of adequate intravenous fluids. This patient's blood pressure had a tendency to drop to shock levels for protracted periods of time, and no doubt this was an important contributing factor.

Patients II, III, IV, and V showed an immediate increase in urinary output following injection. However, at the same time they were receiving .85 per cent saline intravenously. Patients II and III had a sec-

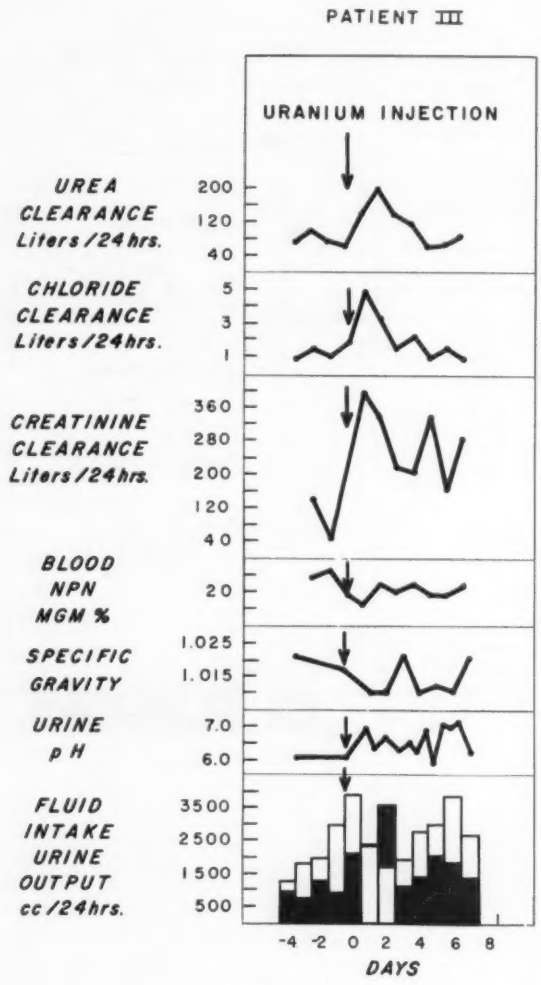

FIG. 8

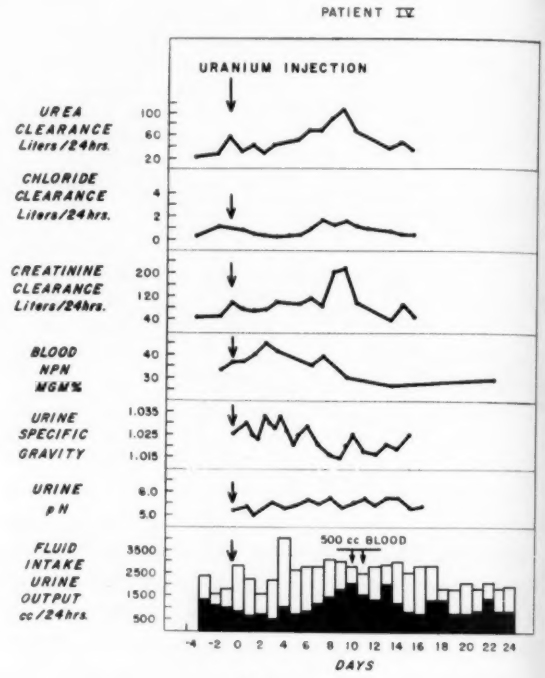

FIG. 9

ond diuresis in response to more intravenous fluids. In the case of Patient II this was delayed until over 2,000 cc. had been administered.

The values for pH and specific gravity on the hourly specimens fluctuated in accordance with the output. All the patients were able to acidify to below pH 6 and concentrate their urine with a specific gravity greater than 1.020 when the hourly output became low.

The twenty-four hour fluid balances revealed a greater output than intake in Patients II and III for two days following injection. Patients IV and V showed evidence of a slight decrease in output; the lowest output being 500 cc. on the second day in the case of Patient IV. During the third day, this patient received supplemental intravenous fluids increasing the in-

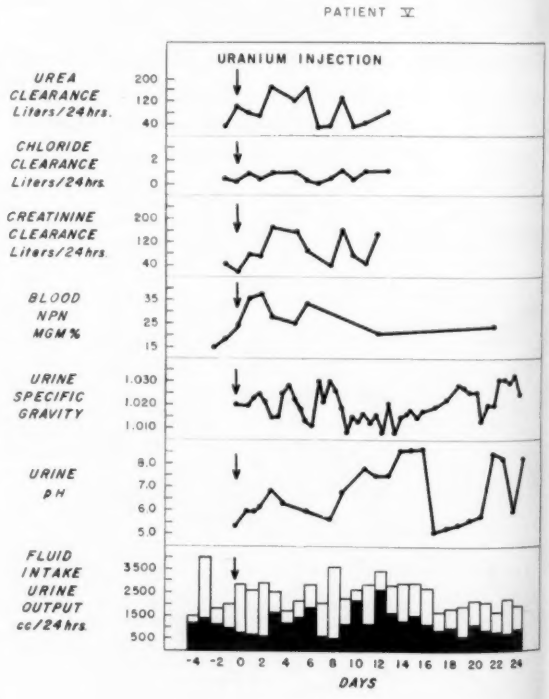

FIG. 10

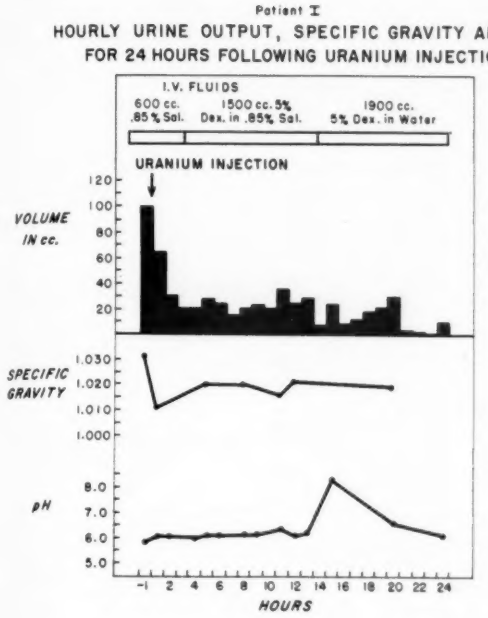

Fig. 11

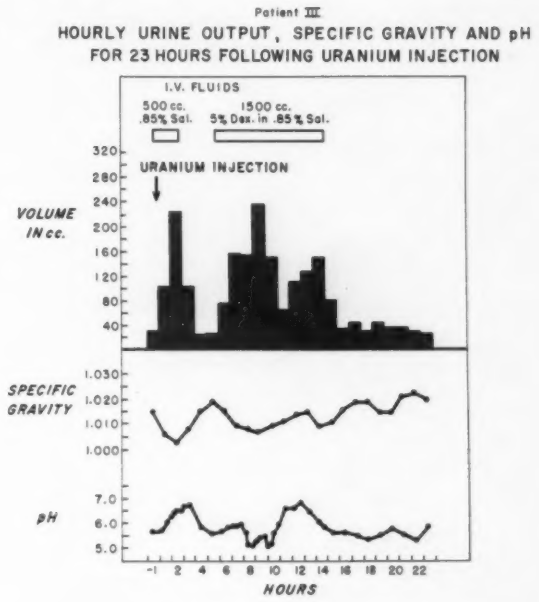

Fig. 13

take to 4,000 cc., but this failed to be reflected in the output.

The curves illustrating the twenty-four hour clearances of chloride, urea, and endogenous creatinine failed to reveal any decrease below control values. However, in the face of unaltered clearances, high specific gravity, and low pH of urine, Patients IV and V showed a significant rise in nonprotein nitrogen during the first three days after injection. These elevations coincided with the periods of decreased urinary out-

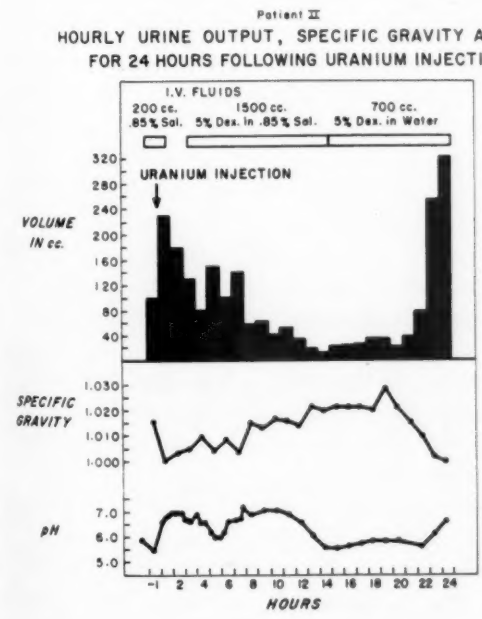

Fig. 12

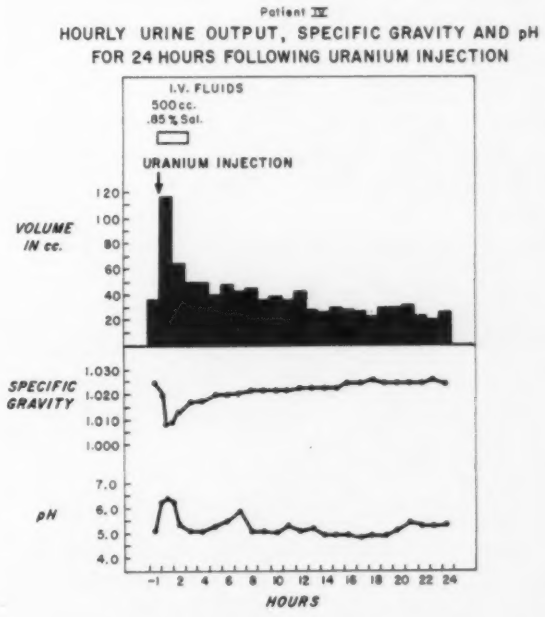

Fig. 14

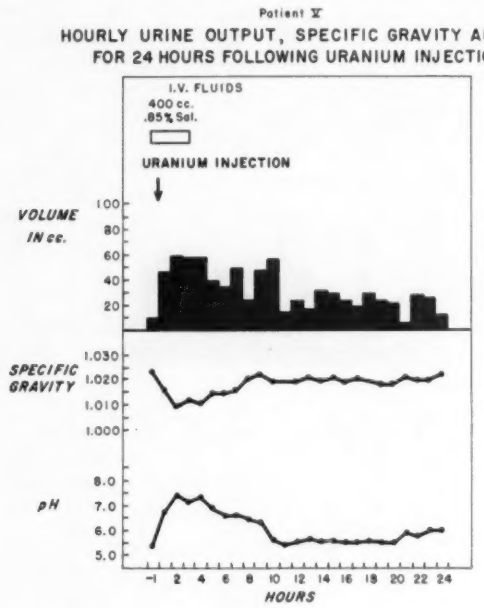

FIG. 15

put and a decline in the clearances of urea and creatinine manifest immediately post-injection.

Serum Electrolytes, Protein, Alkaline Phosphatase, and Amylase. These determinations are shown graphically in Figures 16 to 18. With the exception of Patient v, there was a slight but consistent decrease in serum sodium to below normal values. A

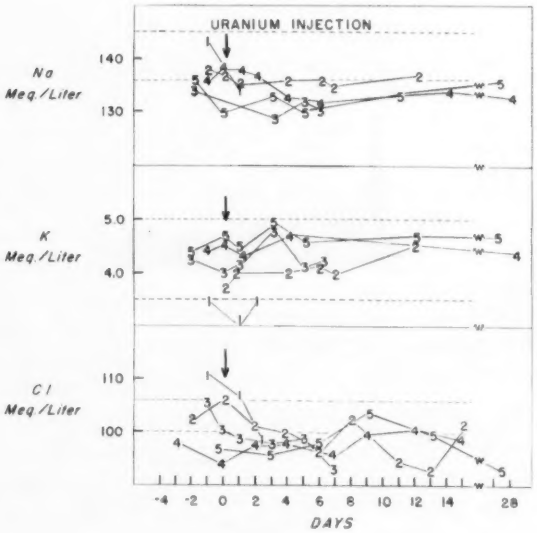

FIG. 16

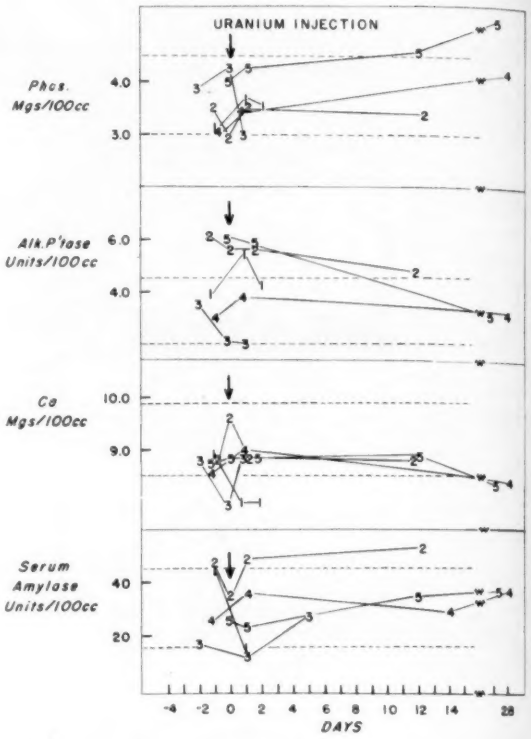

FIG. 17

similar drop in serum chloride was noted for all except Patient IV. A rise in potassium during the first five days was seen in all the patients. Patients IV and V showed a rise in phosphorus and a decline in calcium several weeks after injection. The total protein was low for all the patients except Patient I and remained so for the duration of observation. The serum globulin, pH, and CO_2 showed no consistent changes. The initially high values for alkaline phosphatase in Patients II and V dropped toward normal following injection. The postinjection serum amylase values remained essentially within the normal range with the exception of Patient II, who had an elevation slightly above normal on the first day following injection which was again noted on the twelfth day.

Urine Glucose and Ketone Bodies. Daily testing of the urine of all the patients during the period of observation failed to reveal the presence of glucose or ketone bodies.

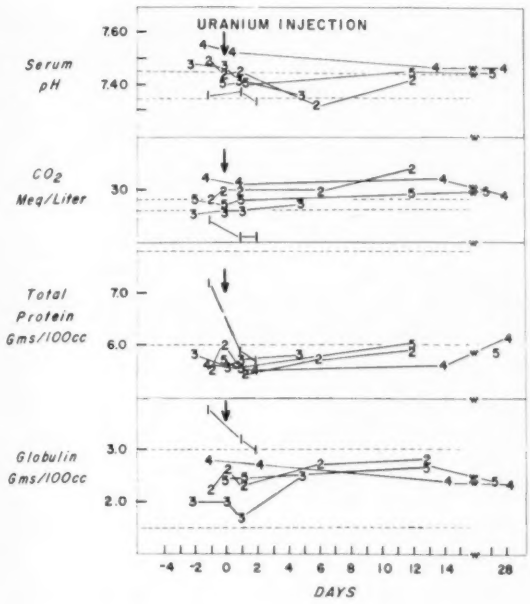

Fig. 18

Pathologic Findings. The final anatomic and microscopic diagnosis on all the patients except Patient IV, for whom autopsy permission was not granted, are given below. Two separate opinions concerning the microscopic examination of the kidneys are listed.*

Patient I

1. Kidney: (A) Congestion; a small venous thrombosis; occasional cast in lower nephron, especially collecting tubules. (B) Albuminous casts present in collecting tubules and a few containing clumps of polymorphonuclear leukocytes; a questionable acute pyelonephritis.
2. Necrotizing bronchopneumonia with septicemia.
3. Phlebothrombosis, left femoral and iliac vessels with extension to the vena cava.
4. Pulmonary emboli, small, with infarction.

* We are grateful to Dr. Robert F. Scully of the Department of Pathology of the Massachusetts General Hospital and Dr. Kenneth Mallory of the Mallory Institute of Pathology of the Boston City Hospital for their review of these slides.

5. Glioblastoma multiforme, right frontal lobe.

Patient II

1. Kidney: (A) Mild nephrosclerosis; hyaline casts in collecting tubules. (B) Epithelium of convoluted tubules somewhat swollen and containing numerous fine hyaline droplets. No other abnormality noted.
2. Alveolar adenocarcinoma of both lungs, with metastases to heart.
3. Fatty metamorphosis of liver.
4. Intussusception of ileum, agonal.
5. Chronic ulcer of esophagus.
6. Cachexia.

Patient III

1. Kidney: (A) No abnormality seen.
2. Recurrent glioblastoma multiforme, left parietal lobe.
3. Bilateral bronchopneumonia.
4. Leiomyoma, 1 cm. in diameter, in wall of first portion of duodenum.
5. Multiple neurofibromatosis with café au lait spots (Von Recklinghausen's neurofibromatosis).

Patient V

1. Kidney: (A) Very mild focal chronic pyelonephritis; question of some edema of the medulla. (B) Changes in convoluted tubules similar to Patient II and also no other abnormalities.
2. Astrocytoma of the left temporoparietal lobe.
3. Bronchopneumonia, bilateral, lower lobes.
4. Encrusted cystitis, chronic.
5. Multiple decubitus ulcers.
6. Atrophy of testicles.
7. Cachexia.

DISCUSSION

Before discussing the significant findings of this study, it is pertinent to review briefly the observations made on these patients concerning the distribution and excretion of hexavalent uranium and the

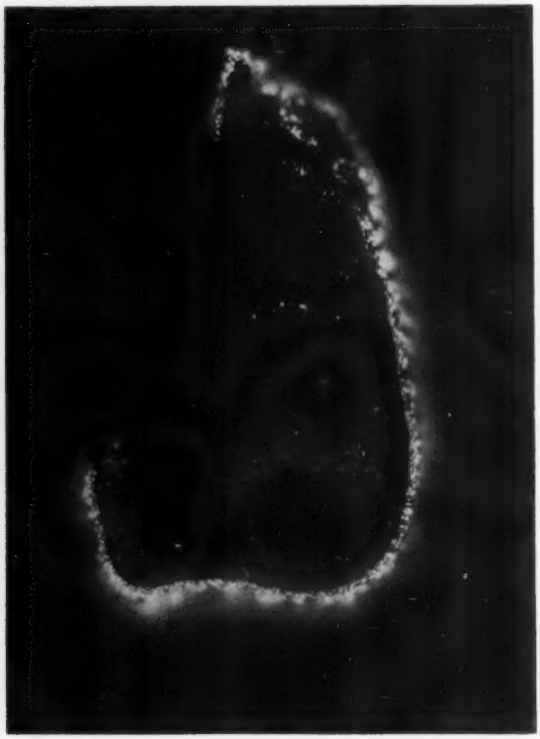

FIG. 19. A gross autoradiogram of a kidney from Patient v, showing greatest concentration of the uranium in the cortical zone.

extensive small mammal studies concerning the mechanism of toxicity.

The distribution and excretion in man[8] was found to be in good agreement with the small mammal data.[11] The injected hexavalent uranium rapidly leaves the blood stream, 99 per cent of the dose being cleared in about twenty hours. In small animals this degree of clearance requires only two to five hours. However, the data pertaining to the fractions of the injected dose initially deposited in the major sites, *i.e.*, the bone, kidney, and urine, coincide more closely. Neuman and Neuman[5] state that the data in rats show 5 per cent to 20 per cent of the dose deposited in the skeletal system, about 20 per cent in the kidney, and 50 per cent to 75 per cent excreted in the urine during the first twenty-four hours following injection. The comparable human data are 6 per cent to 14 per cent deposited in the skeletal system, 16 per cent in the kidneys, and 49 per cent to 84 per cent excreted in the urine.

The specific locus of deposition within bone and kidney is identical in man and the small mammals studied. The uranium first becomes deposited along the luminal surfaces of the proximal convoluted tubules in the outer and midzones of the cortex. Following this, it associates with cellular debris in the lumens of the tubules. The gross autoradiograms of Tannenbaum, Silverstone, and Koziol[10] confirmed the cortical distribution in the kidneys of rats. A gross autoradiogram of a kidney from Patient v is shown in Figure 19. Here, as in the other observations, the uranium is nonuniformly distributed, being more concentrated in the cortical zone. Figure 20 shows a microscopic autoradiogram from Patient v. This indicates that the uranium atoms are associated with cast formation in the lumen of a tubule. This mode of renal deposition was a constant finding, thus confirming the small mammal observations.

The characteristics of bone deposition have been demonstrated by the gross autoradiograms of rat femurs prepared by Tannenbaum, Silverstone, and Koziol,[10] and Neuman and Neuman.[5] A periosteal and endosteal locus is clearly depicted in these, and the scattered spots of activity in cancellous bone suggest a deposition within the haversian system as well. Autoradiograms from a femur of Patient 1 are shown in Figure 21. The characteristics of deposition appear to be identical to those of the rat.

The inference from small mammalian studies[11] is that following injection the uranyl cation is distributed mainly between two complexes, one with the bicarbonate and the other with the protein of the plasma—approximately in equal amounts with each when the CO_2 combining power is normal. The uranyl bicarbonate complexes pass through the renal glomeruli, and as the pH of the glomerular filtrate decreases and the bicarbonate becomes absorbed by the cells of the proximal convoluted tubule, the uranyl cations are liberated to combine with the protein along the tubular wall. That the distal portion of the proximal

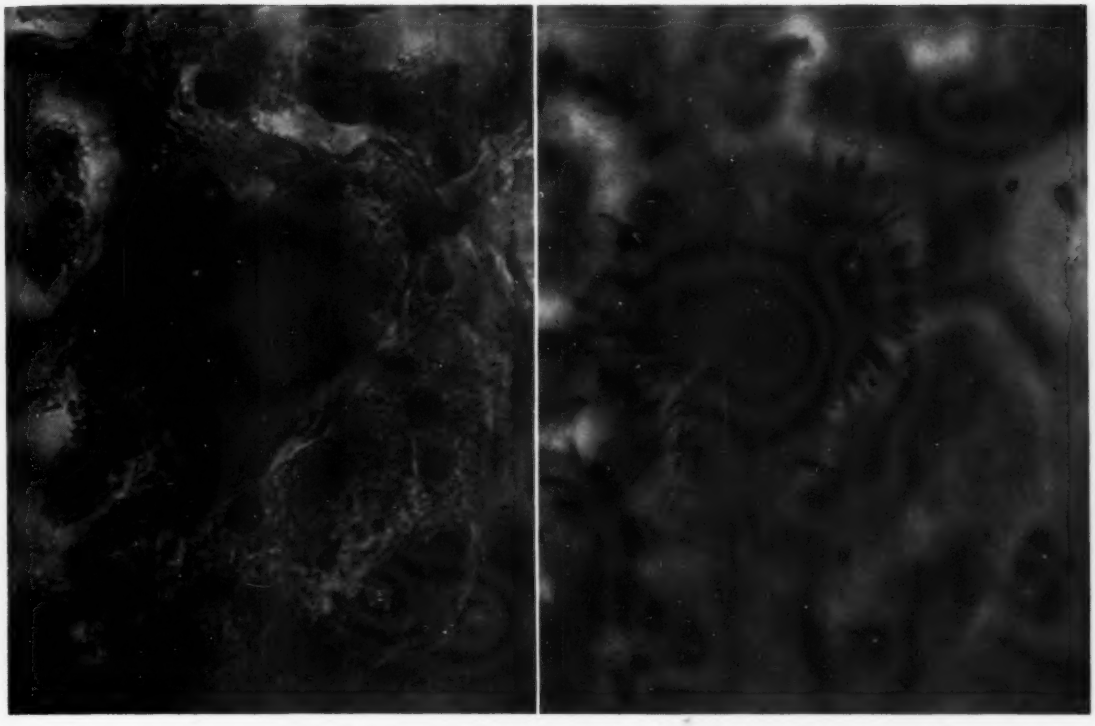

Fig. 20. A microscopic autoradiogram of a kidney section from Patient V, showing a cluster of α tracts associated with debris within the lumen of a renal tubule.

convoluted tubule is the locus of initial damage is confirmed by pathologic examination of the kidneys and clearance data.

The physiologic consequences of the juxtaposition of a high concentration of uranyl cations and the epithelium of the proximal convoluted tubule are apparent immediately. Bicarbonate, chloride, glucose, and amino acids, which are mainly dealt with in the proximal convoluted tubule, appear in the urine in greater abundance. There is an immediate diuresis which, with large doses of uranium, may rapidly decrease to oliguria or anuria. Substances such as urea and NH_4, which are handled by other tubular portions, and creatinine, inulin, and xylose, the excretion of which depends upon glomerular filtration, are unaffected when the damage is not severe.

Numerous studies[11] have shown that minimal effects upon the tubular cells can lead to the loss of protein and enzymes, such as catalase and phosphatase which are abundant in these cells, before the metabolic functioning of these cells is seriously jeopardized. Upon this characteristic depends the increased appearance of these substances in the urine, serving as a sensitive index of tubular damage.

Efforts to elucidate more specifically the mechanisms of toxicity of uranium have led to numerous *in vitro* and *in vivo* metabolic and biochemical studies. *In vitro* studies have demonstrated protein precipitation and the reversible inhibition of certain enzymes, most particularly phosphorylase. The high concentration in the tissue fluids of anions forming complexes made the *in vivo* conditions less suitable for enzyme inhibition studies. However, various metabolic effects unrelated to the renal effects have been described. These include elevated and prolonged glucose tolerance curves and interference with muscle glycogen formation in dogs and rats, elevation of blood inorganic phosphorus in rats, a slight decline in serum protein in rats, changes in the unsaturation of phospholipids of the blood, liver, and kidney

FIG. 21. A gross autoradiogram of the proximal end of a femur from Patient 1, showing periosteal and endosteal concentration and scattered foci of concentration in the cancellous bone consistent with deposition in the haversian system.

in rats, and an increase in blood cholesterol in dogs and rats. Other alterations more related to hepatic function include: decreased efficiency to remove bromsulphalein from the blood, increased excretion of ketone bodies and free phenol, decreased plasma levels of fibrinogen and prothrombin, failure in the conversion of injected lactate into liver glycogen, and some evidence for an increase in total liver lipids.

These findings indicate that it is unlikely that enzyme poisoning, aside from that in the kidney, participates to a significant degree in acute toxicity. This is consistent with the over-all picture of the distribution, excretion, and chemical properties of the uranyl cation. Surface proteins of the cells are only briefly and minimally exposed to uranyl cations after intravenous injection because of the abundance of complexing agents in the tissue fluids and the rapidity with which the cation is cleared

from the soft tissues. The lumen of the renal tubule affords a unique situation where the uranyl cation is present in comparatively enormous concentration for a longer period and with a relative decrease in complexing agents.

To offset this general scheme of the mechanism of toxicity of the uranyl cation, a particular species would have to possess an essential enzymatic system considerably more sensitive than the enzymatic systems in the renal tubules. This is extremely unlikely, especially in view of the evidence that the action of the uranyl cation on the cell surfaces of the tubules is quite general, being more related to concentration than to a specific enzymatic poisoning.[11]

In numerous small mammal experiments[11] it was demonstrated that urinary catalase has a marked consistent rise following uranium intoxication. The comparative ease of quantitative manometric determination has made the test of great value in animal studies. Studies of the catalase activity of normal human subjects[11] showed a mean value of 4.12 cc. O_2/0.2 cc. urine with the huge standard deviation of 9.37. Because the normal subjects occasionally showed values as high as 50 cc. O_2/0.2 cc. urine, such sporadic elevations were not considered as definitely abnormal. Patients with various types of chronic renal disease showed values above normal in several cases, but the findings were not striking and there was no correlation with proteinuria. Therapeutic doses of mercuhydrin, salyrgan, and mapharsen failed to produce catalasuria or proteinuria in humans but caused catalasuria in proportionally larger doses in animals. Exercise sufficient to cause a significant proteinuria in humans failed to produce catalasuria.

That the source of urinary catalase is the tubular cells rather than increased clearance from the plasma was quite conclusively demonstrated by experiments in which it was found that variations in catalase clearance were not correlated with variations in inulin clearance, and increasing the plasma catalase in uranium poisoned animals did not increase the urinary catalase.[11] The urinary protein, which was found to accompany the catalasuria in animal studies, was found by electrophoretic testing to be derived from plasma protein to a large extent. Since pathologic studies failed to reveal evidence of glomerular damage, the method by which the protein gets into the urine can only be hypothesized.

Following moderate doses of uranium in rabbits and dogs, the catalase elevation reached an initial peak within two to three hours and a maximum within three to six days and then a return to normal in several days.[11] As an indication of the sensitivity of the catalase test, it was found that intravenous doses as small as 0.005 and 0.01 mg. U/kg. in dogs and rabbits can evoke increased catalase excretion within a period of two to four days. In the case of rabbits, this was one-tenth to one-twentieth of the lethal dose. Also with rabbits it was shown that small doses can evoke catalasuria without proteinuria, and with larger doses the catalasuria appears before proteinuria and elevation of nonprotein nitrogen. Hence, catalasuria is a more sensitive indicator of tubular damage in the rabbit (and probably in the cat, but only in some of the dogs tested). Also, the catalase test was more specific, reproducible, and had a much greater relative change in all the animals.

The elevation in urinary catalase on the first postinjection day noted in Patient III did not exceed a control value, and the presence of normal values for the subsequent seven days suggested that the tubular effect was insufficient to produce the release of catalase. Also there was no evidence that the injection provoked an albuminuria. In Patients II, IV, and V, who received the largest doses, there was an elevation of both albumin and catalase, with the peaks generally coinciding in Patient II but slightly preceding the catalase peaks in Patients IV and V. With increasing dosage, the magnitude of the albumin peaks became greater. The maximum possible manometric reading using

undiluted urine was approached by all 3 patients, this being about 160 cc. O_2. In Patients IV and V, in whom diluted samples of urine were tested, the catalase peaks were higher in Patient V, who received the larger dose. It has been shown that urine inhibits catalase by approximately 50 per cent when compared to distilled water, and this is the most likely explanation for the higher values obtained with diluted samples.[11] Although catalasuria and albuminuria both appeared in these 3 patients, the catalase peaks represented a far greater relative increase.

As an explanation for the double peaking of catalase values observed in animals, it was suggested that the first peak, occurring about two hours after injection, resulted from an increase in the membrane permeability of the tubular cells, and the second peak, occurring in two to five days, from actual breakdown of the cell structure. There was a definite tendency for double peaking in these patients, being most obvious in Patient V who received the largest dose. However, although the appearance of the maximum peaks corresponded with the animal studies, the initial peak was delayed for one and a half to three days. An explanation for this may be the slower rate of clearance noted in the human studies, or that these patients received relatively smaller doses than the animals studied.

Other evidence of tubular damage is the appearance of casts in Patients IV and V during the period of albuminuria and catalasuria. Patient V had many cellular and coarsely granular casts on the second day, indicating that actual cellular destruction was taking place. This corresponds to the initial catalase peak. At the time of maximum catalasuria on the sixth day, only finely granular casts were noted. This is a fragment of evidence against the concept that the initial peak results from increased permeability of the tubular cell membrane and the maximum peak from cellular destruction. More conclusive data on this point could be obtained by more frequent and quantitative cast determinations.

The extent to which this tubular damage, as manifested by catalasuria, albuminuria, and casts, is reflected in renal function is not entirely clearcut. During the first twenty-four hours following injection, there did not appear to be any tendency for diuresis beyond that expected from the effects of the intravenous fluids.[7] Also the increased urinary outputs of Patients II and III during the first two days are consistent with the excess of intravenous saline received on the day of injection. Patient IV had a definite decrease in output for six days following injection, but during this time the specific gravities ranged from 1.020 to 1.035, making it doubtful that this represented oliguria secondary to renal damage.

All the patients showed a tendency for a more alkaline urine following injection. That this could be due to loss of base with the uranyl cation excretion is not likely because the tendency is not apparent during the initial twenty-four hours when approximately 99 per cent of the dose is excreted. There was a decline in serum pH in all the patients except Patient V, suggesting some interference with the renal capacity for excreting acid, but the serum CO_2 showed no significant change.

During the time of maximal renal effect, as evidenced by albuminuria and catalasuria, there was an elevation of serum potassium, a drop in serum sodium for all except Patient V, and a drop in serum chloride for all except Patient IV. That these changes are not related to the uranium is suggested by the failure of the degree of change to be correlated with the magnitude of the dose and the participation in these changes of Patient III, who failed to show a significant catalasuria or albuminuria. Also, patients with brain tumors occasionally show electrolyte abnormalities. On the other hand, these changes tend to return to control levels as the apparent renal effect wears off. Therefore, they stand as suggestive evidence of an interference with the renal capacity for sodium and chloride reabsorptions and potassium secretion. It is not as likely that the potassium elevation

reflects loss from damaged body cells, because this would be expected at a time when the concentration of the uranyl cation is highest in the body fluids, *i.e.*, for a few hours after injection.

The apparent renal damage was of insufficient magnitude to alter urea and creatinine clearances. It is known that disappearance of several hundred thousand of the circa 2,500,000 nephrons normally present cannot be detected by these tests. As demonstrated by more recent uranium toxicity studies, the tubular capacity to deal with such substances as glucose, vitamine C, and amino acids affords a much more sensitive index of primary tubular damage. However, none of the patients showed glucosuria. Although there were no instances where the urea and creatinine clearances fell below the control values, both Patients IV and V had elevations of blood nonprotein nitrogen with peaks exactly coinciding with the peaks of catalasuria and declines in the magnitudes of the urea and creatinine clearances. However, all these changes also follow the fluctuations in urine output, which are known to influence these factors greatly. The chloride clearances showed no tendency to increase, indicating preservation of the normal capacity to reabsorb this ion. This finding, however, is in conflict with the finding of declines in the level of serum chloride.

Other changes unrelated to renal function which are worthy of note are the development of extrasystoles by Patient IV, a slight elevation of serum amylase in Patient II, elevation of cephalin flocculation above normal on the first postinjection day in Patients II and III, and elevation of serum phosphorus and decline of serum calcium in Patients IV and V several weeks after injection. These changes are not consistent, nor do they deviate from what might be expected in patients in this clinical condition. Therefore, it is not likely that they are ascribable to the uranium injection.

All the patients with the exception of Patient I expired after the time in which the acute tubular effects would be apparent pathologically. The findings described are not beyond those often seen in terminal patients. There was no evidence of atypical tubular cells as described by Oliver[6] in dogs. Since Patient I was showing hyaline casts prior to injection, the casts observed pathologically cannot be attributed to the uranium effect. The tubular cells in this patient failed to show evidence of toxicity.

The alveolar adenocarcinoma found in Patient II was obviously of longer duration than the sixty days that elapsed following the uranium injection, and, therefore, was unrelated. The diagnosis of multiple neurofibromatosis had been made on Patient III prior to injection.

CONCLUSIONS

The toxicity of hexavalent uranium injected intravenously in humans in the dosages employed is readily apparent by a catalasuria and albuminuria which show an initial peak during the first one and a half to four days and a second one at the sixth to eighth day. The minimal dose necessary to produce this effect is of the order of 0.1 mg. of uranium/kg., and with increasing dosage the effect becomes greater. The relative increase in catalase is far greater than that of albumin. Further evidence of tubular damage is indicated by the appearance of cellular casts which can appear as early as the second day. Concomitant with this tubular damage there is suggestive evidence of interference with the renal capacity for reabsorption of Na and Cl and the secretion of potassium. There is no good evidence of a diuretic effect at this dosage. There is a tendency for a more alkaline urine. As evidenced by declines in the twenty-four hour clearances of urea and creatinine, it is suggested that a sufficient number of nephrons were incapacitated to cause a transient rise in serum nonprotein nitrogen with the doses of 0.17 and 0.28 mg. uranium/kg. Impairment of tubular function was of insufficient degree to allow glucosuria at normal blood glucose levels. Evidence for toxic manifestations in other systems or unrelated to

renal abnormality was lacking. The tubular changes were of insufficient degree to be pathologically detectable after forty-two days, and as early as 2.4 days when the dosage was 0.097 mg. uranium/kg.

The findings permit an estimation of man's relative position with the rabbit, guinea pig, rat, and mouse in regard to approximate lethal dosage. He is certainly more tolerant than the rabbit and guinea pig, which usually succumb with doses of 0.1 and 0.3 mg. uranium/kg. In the rabbit, catalasuria commences at approximately one-tenth the lethal dose. If this is carried over to man, it indicates a lethal dose of about 1 mg. uranium/kg., which is the range of the rat. The findings are against human toleration as high as 10 mg. uranium/kg., which is the lethal dose of the mouse.

SUMMARY

Five terminal patients with brain tumors were given intravenous injection of uranyl nitrate in doses of 0.097, 0.12, 0.07, 0.17, and 0.28 mg. uranium/kg. The 3 patients receiving the largest doses showed an elevation of urinary catalase and albumin. Other evidences of renal toxicity were the appearance of casts in the urine and elevation of nonprotein nitrogen. There was suggestive evidence of the loss of renal capacity for sodium and chloride reabsorption and potassium secretion. Electrocardiograms, liver function studies, hematologic tests, and glucose tolerance tests failed to reveal other evidences of toxicity. Four of the patients who came to autopsy did not reveal any unusual findings. Of the common laboratory animals, man appears to correspond most closely to the rat in regard to intravenous tolerance to uranium.

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VOL. 79, NO. 1

EPIDERMOID CARCINOMA OF THE LOWER LIP*

RESULTS OF RADIATION THERAPY OF THE LOCAL LESION

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THIS study was undertaken to determine the efficacy of radiation therapy for the local lesion in a series of 519 cases of epidermoid carcinoma of the lower lip. It is obvious that some of the cases with controlled lesions died of metastatic spread and these will be reported as such, but our major interest was the study of the end results of treatment on the local lesion itself.

MATERIAL

In a twenty year period from 1931 to 1951, 519 consecutive unselected cases of epidermoid carcinoma of the lower lip were treated by irradiation at the State University of Iowa Hospitals. The data presented are based on a review of this material and comparison with similar series in the literature. Factors which were considered in reviewing these cases included size, location and pathology of the lesion, age distribution, previous definitive treatment, presence of metastases, method of treatment of local and metastatic disease, and results of treatment.

CLINICAL FEATURES

Incidence. Carcinoma of the lower lip is not an uncommon disease. It constituted five per cent of the total cancer admissions to this hospital during the period under review. This figure is probably not representative of the actual incidence of the disease, since most of our cancer admissions were those requiring extensive diagnostic and therapeutic procedures. Other reports indicate a variation from 2 per cent to 11 per cent of cancer admissions. This lesion constitutes approximately 25 to 30 per cent of all oral carcinoma.

Age, Sex, Race. The youngest patient was twenty-three years of age and the oldest ninety-three, with the maximal incidence between the ages of sixty and seventy (Fig. 1). The incidence in females was low. This is consistent with previous reports. Only 16 females, or 3.1 per cent, are included in this series. The incidence in females in other reports varies from 0 to 16 per cent. None of our cases was a Negro, but the Negro population is quite low in this area.

Pathology. In our opinion it is desirable to have a biopsy of every lesion. However, a certain number of our patients refused this procedure. Another group was referred direct to our department from outside physicians with obvious neoplasm. In still other instances biopsies were obtained, but the tissue was declared inadequate for diagnosis. Three hundred and forty-eight of our cases were proved and 171 clinically diagnosed. Previous studies confirmed the validity of treatment on the basis of clinical diagnosis. Therefore, we have combined these cases with the proved lesions in this series. All cases where there was equivocation as to the malignant nature of the lesion were excluded from the series. Of the biopsied cases, 327 had had well differentiated or undesignated, 13 moderately well differentiated and only 8 poorly differentiated carcinomas.

Previous Treatment. Three hundred and seventy-nine cases presented themselves with lesions which had had no previous treatment to the involved area. The re-

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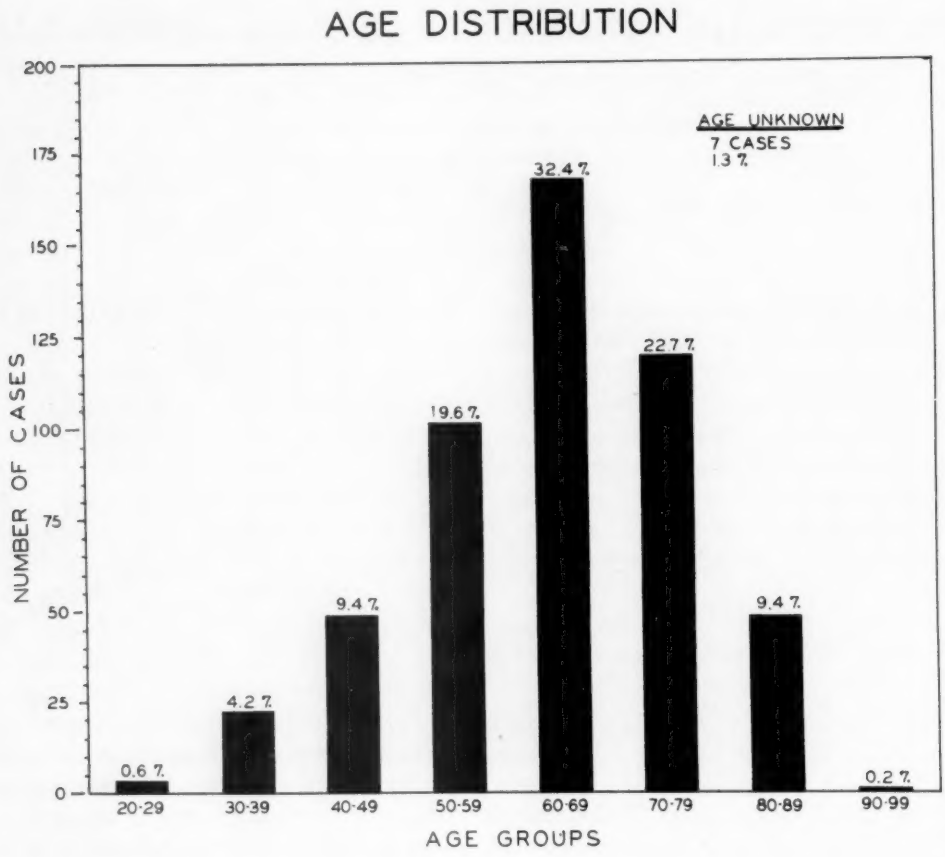

FIG. 1.

maining 140 cases had had some form of definitive therapy prior to being seen by us. These had undergone one or more attempts at treatment with subsequent recurrence. This therapy consisted of excision, electrocautery, caustic, acid, radium, roentgen ray or a combination of these methods (Table I).

Size and Location. The size and location of the lesion were recorded in all instances. Figure 2 illustrates the location of the lesion. The shaded portions indicate the areas of involvement: angle—lateral—middle—lateral—angle. No effort has been made to lateralize the lesion to the right or left. The lesions varied in size from those less than 0.5 cm. in diameter to some involving the entire lower lip, both angles of the mouth and extending to buccal mucosa, cheek and chin (Table II).

TREATMENT

Local Lesion. Only the methods of treatment incorporating some form of radiation are considered here. Cases in this series have been irradiated with 200 kv., 0.5 mm. Cu filtered roentgen rays, corresponding to a half-value layer of 0.95 mm. Cu; 133 and 120 kv., unfiltered or 1.0 mm. Al filtered roentgen rays; 60 kv. unfiltered roentgen

TABLE I

PREVIOUS TREATMENT

Type	No. of Patients	Per Cent
Excision	43	8.3
Caustic, acid or cautery	42	8.1
Roentgen therapy	49	9.5
Radium therapy	6	1.1

TABLE II

SIZE OF LESION

Size	No. of Patients	Per Cent
Less than 1.0 cm.	30	5.8
1.0 to 2.0 cm.	232	44.7
2.0 to 3.0 cm.	92	17.7
3.0 to 4.0 cm.	65	12.5
Over 4.0 cm.	100	19.3

rays using the Chaoul contact apparatus; radium mould; interstitial radium implantation and combinations of these methods (Table III). In recent years the treatment of the local lesion has been almost exclusively with either 120 kv. unfiltered or 1.0 mm. Al filtered roentgen rays, or 60 kv. unfiltered contact roentgen rays. We have found that these two forms of superficial irradiation are as effective as the other forms mentioned above; they are much more flexible, less time consuming, require fewer protective measures and produce better cosmetic and functional results. The Chaoul contact apparatus offers certain advantages in selected lesions. These include greater flexibility, lower dose in the tissues beneath the lesion, fewer protective measures, and larger daily dose with a consequent shorter course of treatment. We believe, however, that satisfactory treatment can be given to any case of carcinoma of the lip without the use of a contact machine.

TABLE III

TYPE OF TREATMENT

	No. of Patients	Per Cent
Contact roentgen therapy	224	43.2
Superficial roentgen therapy	196	37.8
Deep roentgen therapy	17	3.3
Radium therapy		
Plaque	22	4.2
Interstitial	5	0.9
Combination of above methods	55	10.6

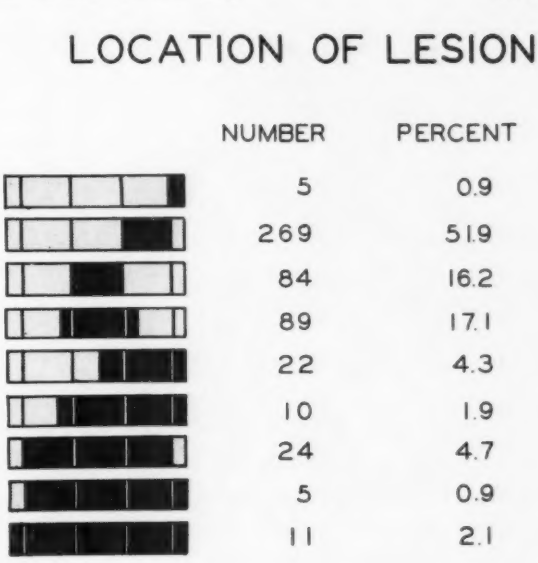

FIG. 2.

The dosage schedules are outlined according to the nature of the lesion. Small superficial lesions can often be treated adequately with a single dose of unfiltered radiation. The massive lesions which involve a large portion of the lip and adjacent structures may require treatment over a three-week period, using two fields and 1.0 mm. Al filtration. We have never used treatments at weekly intervals, as practiced by some authors, because of our concept of dose-time relationships.

In general, the plan of treatment which we use is as follows:

1. A superficial lesion 0.5 cm. in diameter is treated with a single dose of 2,500–3,000 r unfiltered 60 kv. contact roentgen rays.
2. A lesion 1 cm. in diameter is treated with two doses of 1,500 r each using unfiltered 60 kv. contact or 120 kv. superficial roentgen rays, spaced twenty-four to forty-eight hours apart.
3. A lesion 2 cm. in diameter and less then 1 cm. in depth is treated with either 1,000 r in air daily unfiltered 60 kv. contact roentgen rays for a total of 5,000–6,000 r or with 300–500 r

daily unfiltered 120 kv. superficial roentgen rays for a total of 4,500 r.

4. A lesion over 2 cm. in diameter and more than 1 cm. in depth is best treated with 120 kv. superficial roentgen rays which are filtered by 1.0 mm. Al if the carcinoma is bulky. A dose of 300 r is delivered daily to a total of 4,500–5,100 r.

Protection of uninvolved tissue is, unfortunately, often overlooked by some in the treatment of these lesions. The use of a few simple aids spares the patient the discomfort of a radiomucositis of the adjacent tongue, gingiva and buccal mucosa. Packing the lip away from the gingiva and teeth with gauze renders the lip more accessible to the therapy cone. A cutout in lead approximately 0.5 mm. thick will limit the beam to the desired treatment area. A boundary of 0.5 to 1.0 cm. of grossly uninvolved tissue, depending on the nature of the lesion, is included in the cutout. A thin, leaded rubber or 0.5 mm. lead shield is inserted between the lips and gingiva for additional protection. For the best cosmetic and functional result and for the comfort of the patient, proper care of the treated area is essential. Regular application of unmedicated petrolatum, bland oil, cold cream or any other bland emollient to the area during and after treatment has proved most satisfactory. This seems to promote healing and minimize scarring. The patients are specifically warned against the use of proprietary salves and irritating preparations. In addition, they are informed of the permanent increased sensitivity of the treated area to thermal and actinic stimuli. Care is taken to avoid burning the lip with hot foods or tobacco smoke. Excessive sun on the lip may result in ulceration. As many of our patients are farmers, spending long periods in the field, this latter consideration is especially important. They are instructed to wear broad-brimmed hats and cover the lip with one of the preparations mentioned above when exposed to the sun, or a handkerchief may be worn over the lower part of the face. Chapping and fissuring of previously uninvolved areas on the lip are prevented and treated in the same manner.

TABLE IV

METASTASES INITIALLY

	No. of Patients	Per Cent
None	459	88.5
Submental	12	2.3
Submaxillary	37	7.1
Anterior cervical	11	2.1

Metastases. In 412 cases no metastatic disease was demonstrable at any time. Of the remaining 107 cases, 60 or 11.5 per cent of the series, had enlargement of the submaxillary, submental or anterior cervical lymph nodes on their first visit. The remaining 47 patients, or 9.1 per cent of the series, developed metastases subsequent to initial treatment (Table IV).

The lymphatic drainage of the lower lip is via three lymphatic trunks to two groups of lymph nodes. Two trunks drain the lateral portion of the lip to the prevascular lymph nodes of the submaxillary group. The third trunk drains the medial portion of the lip to the submental group. There is a crossing channel between the two trunks draining the medial portion of the lip. This accounts for the occasional metastasis from a lesion near the midline of the lip to the contralateral cervical region.

Carcinoma of the lip metastasizes late and almost invariably follows the direct lymphatic route. This late metastasis is probably best explained by the usual high degree of differentiation of the primary lesion. The first metastasis is to the submaxillary or submental group of lymph nodes, depending on the location of the primary lesion. These lymph nodes will usually attain palpable size before there is further spread. In only 18 of the total of 107 cases with initial or subsequent metastasis, was there evidence of anterior cervical lymph node involvement. A single case was proved to have a distant metastasis. Since metastases are first evident in this area, an inte-

gral part of the patient's care is the careful palpation of the submental, submaxillary and anterior cervical regions.

In our experience and from the experience of the majority of authors concerned with this subject, the treatment of cervical metastasis from carcinoma of the lip is a surgical problem. In the hands of men skilled in the use of interstitial radium, this problem can also be adequately handled by radium implantation. Perhaps the only exception to this rule is the rare, poorly differentiated carcinoma which spreads rapidly and diffusely. In these cases intensive external roentgen therapy to the neck is of value. The sole prerequisite for surgery is the palpation of an enlarged lymph node. Unless there is unequivocal evidence that the lymph node is inflammatory, surgical treatment in the form of supraomohyoid or radical neck dissection is indicated. Simple excision of the lymph node is a procedure which is conducive to local and lymphatic spread of the neoplasm and is probably never indicated. There are instances in which the lymph node metastases are declared inoperable. In these cases there is indication for the use of interstitial radium implantation plus external irradiation, often with very good results.

Another complication of carcinoma of the lip which is considered a surgical problem is involvement of the mandible. This occurs by direct extension from a metastatic lymph node or, less commonly, from the primary lesion itself. A dose of external roentgen therapy sufficient to eradicate the carcinoma within the bone will probably also cause radionecrosis and ultimate slough.

To leave the subject of cervical metastases without explaining the status of prophylactic neck dissection might result in the reader's misinterpretation of our statement, ". . . the treatment of cervical metastasis from carcinoma of the lip is a surgical problem." There are surgeons who advocate routine prophylactic neck dissection for all cases of carcinoma of the lower lip. Since this practice was started, many persons concerned with the problem of treating this disease have questioned the advisability of such a procedure. In recent years very convincing statistical data on the subject have been amassed by both radiologic and surgical authors. The material from several of these sources shows that approximately 6 per cent of the total patients could possibly benefit from the procedure. This figure approaches that of the operative mortality rate reported by some. In other words, 15 unnecessary operations would have to be performed for each one which might benefit the patient. Prophylactic neck dissection for carcinoma of the lip, therefore, seems unjustified.

RESULTS

In compiling the results of the treatment of the local lesion in this series of 519 cases of epidermoid carcinoma of the lower lip, we have used two methods. The absolute survival refers to the number of patients alive at the end of the chosen period. This has been compiled in Table V for both three and five years. The net results have been determined by subtracting the cases with healed primary lesions lost to follow-up and those dead with healed primary lesions from the total cases to give a determinate group on which the statistics are based. Both three and five year net results are presented in Table VI.

Many authors have staged their lesions and presented the results separately for each of the different stages. We found that

TABLE V

ABSOLUTE SURVIVAL

	No. of Patients	Per Cent	
Total	519	100	
Absolute three year survival	385	74.2	
Expected three year survival*			86.3
Absolute five year survival	338	65.1	
Expected five year survival*			77.4

* Institute of Life Insurance, 1939–1941 mortality table.

TABLE VI

NET RESULTS

		Three Year		Five Year
Total		519		519
Indeterminate group				
Dead with healed local lesion	99		139	
Lost with healed local lesion	4		10	
		103		149
Determinate group		416		370
Treatment failures		63		65
Successful		353—84.9 per cent		305—82.4 per cent

TABLE VII

THREE YEAR NET RESULTS RELATED TO SIZE

	Less than 2.0 cm.	Over 2.0 cm.
Total	262	257
Indeterminate group	43	60
Determinate group	219	197
Treatment failures	17	46
Successful	202—92.2 per cent	161—76 per cent

TABLE VIII

THREE YEAR NET RESULTS RELATED TO PREVIOUS TREATMENT

	No Previous Treatment	Previous Treatment
Total	379	140
Indeterminate group	72	31
Determinate group	307	109
Treatment failures	31	32
Successful	276—90.9 per cent	77—70 per cent

by separating the local lesions into two groups, those under 2 cm. in diameter and those greater than 2 cm. in diameter, the total group was divided almost into halves. The three year net results in these two groups are presented in Table VII.

Investigators on this subject have observed consistently poorer results in those cases recurrent after previous treatment. Table 1 shows the number of patients previously treated and the types of previous treatment. In Table VIII, the three year net results in the previously treated and previously untreated lesions are presented.

Of the group which was treated ten years or more prior to the end of the period under consideration, all but 9 had ten year follow-up. These 9 cases were lost without evidence of local recurrence. Of the entire group of

Table IX

COMPARISON OF TWO PERIODS OF STUDY

	Group I 1931–1941		Group II 1941–1951	
	Three Year	Five Year	Three Year	Five Year
Total	328	328	191	191
Indeterminate	62	81	41	64
Determinate	266	247	150	127
Failures	48	50	15	15
Successful	218—82 per cent	197—79.5 per cent	135—90 per cent	112—88 per cent

cases followed from five to twenty years after treatment, there was only 1 case in which recurrence of the local lesion after five years was suspected. As noted in Table VI, only 2 cases of recurrence between three and five years were diagnosed.

Since this series encompasses twenty years of experience, it gives an opportunity to assess any improvement in results which may have taken place during this time. Our dosage schedules and techniques have changed and some difference in results might logically be expected. We have divided the series into 2 ten year periods. Group I includes the cases treated from 1931 through 1940 and Group II includes those treated from 1941 through 1950. The three and five year net results for the two groups are presented in Table IX.

Table X contains the three and five year net and absolute results obtained by a group of radiologic and surgical authors for comparison. For use in this table our results have been recalculated to include deaths from metastatic disease in the determinate group for net results. This, of course, has no relation to the effectiveness of our treatment of the local lesion, but they must be included for sake of uniformity.

It is difficult to tabulate cosmetic results, since they must be seen to be evaluated. We have included photographs of a representative group of patients before and after treatment (Fig. 3–9). All of these patients were followed five years without recurrence. Patient T. C. (Fig. 3) was clinically diagnosed while the remainder were proved by biopsy. A brief outline of the method of treatment is included in the legends.

Table X

COMPARATIVE SERIES

Author	Total	Three Year Absolute	Three Year Net	Five Year Absolute	Five Year Net
		Per Cent	Per Cent	Per Cent	Per Cent
Schreiner and Christy[31]	636	—	—	61	78
del Regato[29]	116	75	83	—	—
Sharp *et al.*[32]	208	—	—	75	94
Wookey *et al.*[40]	1128	—	—	58	85
Ebenius[9]	749	76	82	67	79
Burkell[5]	534	—	—	79	89
H. Martin[24]	375	—	—	58	70
Ward and Hendrick[36]	259	74	—	70	—
Gladstone and Kerr	519	74	85	65	82

FIG. 3. T.C., No. 163, aged seventy-two. Clinically diagnosed epidermoid carcinoma of the lower lip. In a period of seven days 3,500 r, unfiltered, 133 kv. radiation was given. The patient was followed eleven years without recurrence.

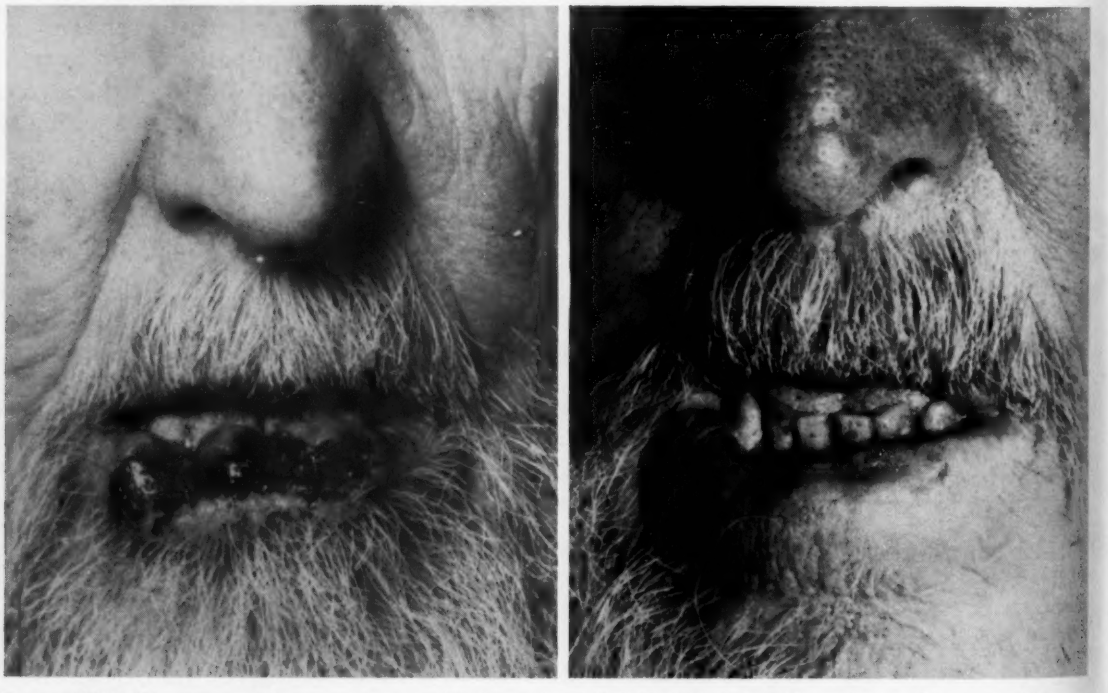

FIG. 4. S.K., No. 154, aged seventy-seven. Moderately well differentiated epidermoid carcinoma on biopsy. In a period of seven days 3,800 r, 133 kv. unfiltered radiation was given. The patient was followed ten years without recurrence.

FIG. 5. R.L., No. 266, aged sixty-five. Well differentiated epidermoid carcinoma on biopsy. In a period of thirteen days 6,500 r, unfiltered, 60 kv. contact radiation was delivered. The patient was followed six years without recurrence.

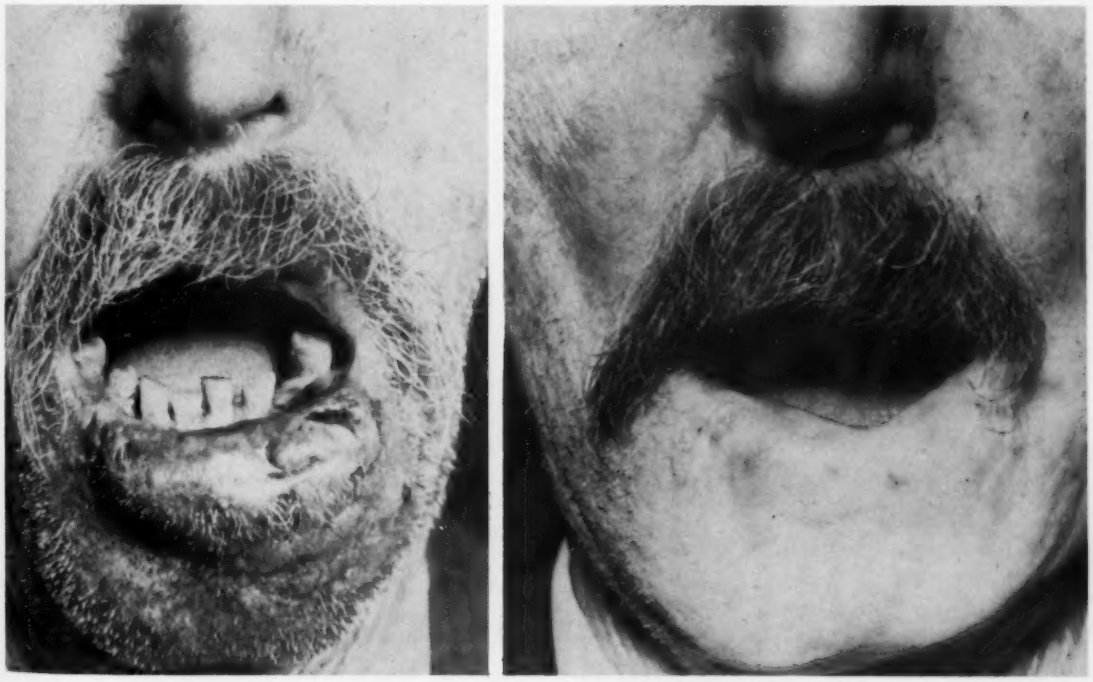

FIG. 6. O.B., No. 279, aged seventy-nine. Well differentiated epidermoid carcinoma on biopsy. In a period of twelve days 3,600 r, 133 kv. unfiltered radiation was administered and supplemented by 2,488 mg. hr. of interstitial radium application. The patient was followed four years without recurrence.

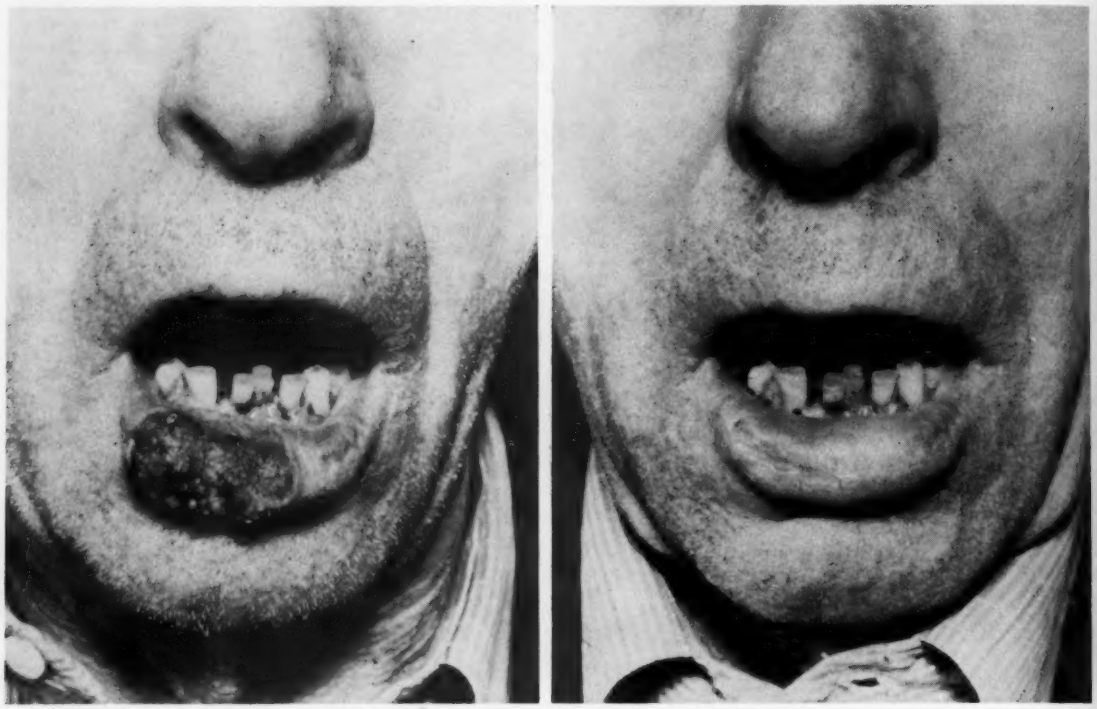

FIG. 7. W.M., No. 316, aged sixty-four. Moderately well differentiated epidermoid carcinoma on biopsy. In a period of fourteen days 4,200 r, unfiltered, 120 kv. radiation was delivered. The patient was followed ten years without recurrence.

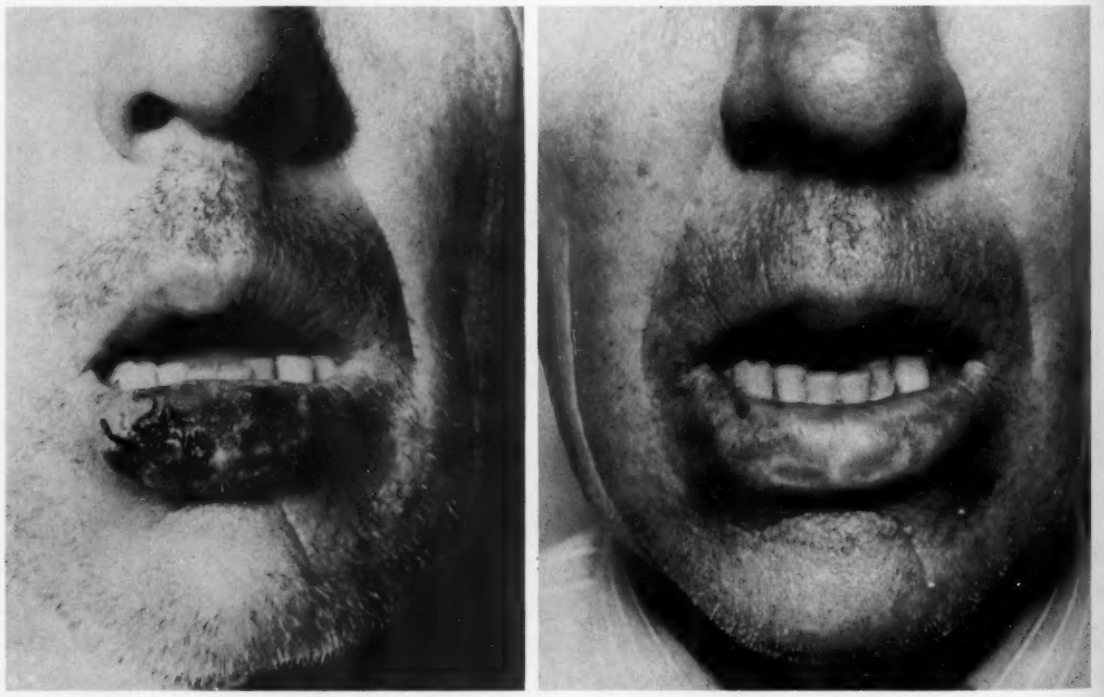

FIG. 8. L.R., No. 330, aged fifty-five. Well differentiated epidermoid carcinoma on biopsy. In a period of nine days 6,000 r, 60 kv. unfiltered contact radiation was delivered. The patient was followed eleven years without recurrence.

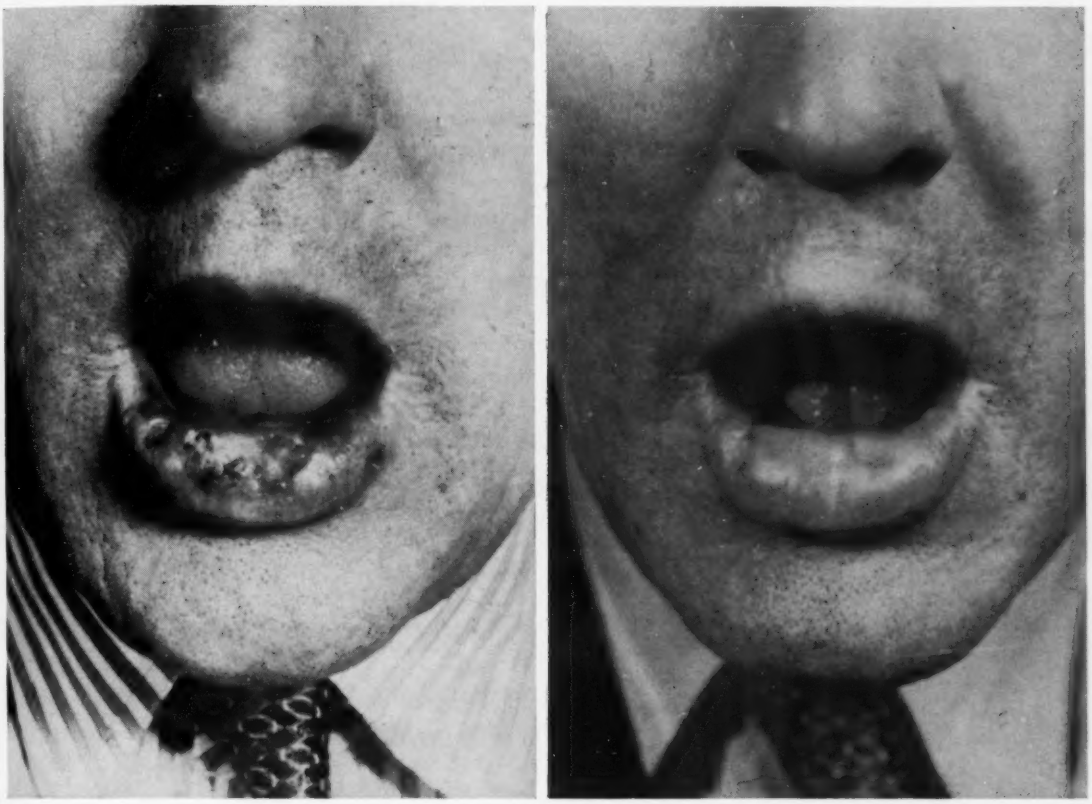

Fig. 9. W.B., No. 343, aged fifty-one. Well differentiated epidermoid carcinoma on biopsy. In a period of six days 6,000 r, 60 kv. unfiltered contact radiation was administered. The patient was followed seven years without recurrence.

DISCUSSION

As indicated by the title and the opening paragraph, the purpose of this report is evaluation of radiation therapy as a treatment of the local lesion in carcinoma of the lower lip. Therefore, in reporting the five year net results, only the instances in which the local lesion was not controlled by our therapy for five years were considered failures. If the patient died of or with metastatic disease before the end of the five year period, he was excluded from the determinate group. The same factors hold for the three year net results. By this procedure the presentation of misleading data is avoided and the inequities of comparing series, some of which contain a far higher percentage of patients with metastatic disease, are eliminated. Since all the series used for comparison (Table x) included deaths from metastatic disease in the group of therapeutic failures, we have compiled our results in a similar manner for inclusion in this table.

SUMMARY

The material for this report consisted of 519 consecutive, unselected cases of epidermoid carcinoma of the lower lip treated by irradiation during the period of 1931 through 1950. Carcinoma of the lower lip constituted 5 per cent of the total cancer admissions to this hospital. The average and mean ages in the series were 62.9 and 64 years, respectively. Three and one tenth per cent of the patients were females. The right or left lateral aspects of the lip were more frequently involved than the midline and involvement of the angle of the mouth was relatively uncommon. The location and size of the lesions are indicated in Figure 2 and Table II.

The techniques of diagnosis, treatment

and care of the treated area are discussed. Contact or superficial roentgen therapy was used in 81 per cent of the cases, deep roentgen therapy in 3.3 per cent and radium in 5.1 per cent with combinations of these techniques in 10.6 per cent.

In 88.4 per cent of the patients there were no demonstrable metastases at the time of the first visit. The remainder had submental, submaxillary and anterior cervical lymph node involvement with only 1 instance of a distant metastasis developing. Our concepts of the care of metastatic disease are discussed.

The absolute three and five year survivals were 74.2 per cent and 65.1 per cent, respectively. More significant, with respect to control of the local lesion, were the net results showing a three year cure rate of 84.7 per cent and a five year success of 82.8 per cent. In only 2 instances was a recurrence suspected between three and five years. Size and previous treatment of the local lesion had considerable effect on the success of therapy. The lesions under 2.0 cm. in diameter had a three year cure rate of 92.2 per cent, while those over 2.0 cm. showed a 76 per cent satisfactory response. If previous treatment by surgery, cautery, caustics or irradiation had not been used, the three year successful treatment rate was 90.9 per cent. In the 140 patients in which one or more of these agents had been employed previously, our results dropped to 70 per cent.

In an effort to evaluate any improvement in results with modified irradiation techniques introduced in later years, the series was divided into 2 ten year periods. The three and five year net results for the 328 cases treated from 1931 through 1940 were 82 per cent and 79.5 per cent, respectively. In the 191 cases from 1941 through 1950 these figures rose to 90 per cent and 88 per cent respectively.

The results of some of the recent, larger series, reported in the literature are offered for comparison in tabular form (Table x).

CONCLUSIONS

1. Radiation therapy is as effective in the control of carcinoma of the lower lip as any method now available.

2. Untreated cases of carcinoma of the lower lip show a 30 per cent increase in response to radiation therapy over those which recur after an attempt at definitive therapy.

3. The cure rate in carcinoma of the lower lip decreases with increase in size of the lesion.

4. Metastasis from carcinoma of the lower lip follows a direct lymphatic route with extremely rare spread beyond the anterior cervical chain of lymph nodes.

5. A three year cure rate is statistically significant in carcinoma of the lower lip.

6. The cure rate of carcinoma of the lower lip treated by irradiation in the past decade has increased 10 per cent over the preceding ten years.

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A STUDY OF HODGKIN'S DISEASE TREATED BY IRRADIATION*

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IN 1950 a preliminary report[5] was published from the Department of Radiotherapy, Toronto General Hospital on the follow-up of 138 patients with Hodgkin's disease who had been treated radiologically. Most of these patients are included in the present report.

Hodgkin's disease in all its vagaries of site and form presents a puzzling picture. Its misleading similarity to the other malignant lymphomas and to certain nonlymphomatous diseases increases the difficulty of diagnosis. Boeck's sarcoid, tuberculosis and even carcinoma of the thyroid have all been wrongly diagnosed as Hodgkin's disease.

It has been the custom to regard the prognosis of this disease as a tale of unrelieved gloom. One of the objects of this paper is to dispel something of that gloom and to demonstrate the value of early diagnosis, energetic initial therapy and close follow-up of patients suffering from Hodgkin's disease. All cases included received their initial course of irradiation in the Department of Radiotherapy, Toronto General Hospital, formerly under the direction of the late Dr. G. E. Richards and now under the present director of the Institute, Dr. C. L. Ash.

The pathology of all cases of the Institute at any time diagnosed as Hodgkin's disease has recently been reviewed by Dr. William Anderson, Pathologist, Toronto General Hospital, Assistant Professor of Pathology, the University of Toronto. Only cases verified by him as true Hodgkin's disease on review of the original slides have been included in the present series. One exception, however, has been made; in order to ensure a well-balanced series of representative cases, 7 cases of Hodgkin's disease of the mediastinum in which no biopsy had been taken have been included. In spite of the fact that the slides of several of the earlier cases (including some long-term survivals) could not now be obtained for review, the over-all survival rates have not altered appreciably since the report of 1950.[5]

STATISTICAL COMPILATION

Initial Site. The distribution by initial site is recorded in Table I and I-A. It is interesting to note that approximately one-half of the entire group gave a history of involvement of the cervical lymph nodes prior to that of any other site. Of the total number only 9 per cent or 26 cases demonstrated initial involvement of the more rare sites.

Gross Survival Rates. In the present survey (Table II) there are more fifteen and twenty-year survivals for study than were included in the previous report. The fifteen-year survival rate of 25 per cent is significant because of the moderately large number of cases (64) included in that estimate. The twenty-year survival rate is not as significant statistically but is very encouraging. One of the 6 twenty-year survivors has died since of extraneous disease. Another deserves special attention as she has survived twenty-five years without recurrence; she was pregnant on admission for treatment, and had involvement of both sides of the neck. The pregnancy was allowed to terminate at the normal time before treatment was initiated.

At the other end of the scale, one notes that one-third of the 291 cases failed to survive one year. The percentage which failed to survive, or the 34 "percentage loss" during the first year after admission,

* From the Ontario Institute of Radiotherapy, Department of Radiotherapy, Toronto General Hospital.
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TABLE I

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1954
DISTRIBUTION BY INITIAL SITE OF DISEASE
(291 CASES)

Site	No. of Cases	Right	Left
Lymph Nodes			
cervical	151	60	91
mediastinal	37		
axillary	26	10	16
inguinal	22	8	14
abdominal	22		
Other Sites*	26		
Not Known	7		

* See Table I-A.

TABLE I-A

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1954
DISTRIBUTION BY INITIAL SITE OF DISEASE
*OTHER SITES THAN IN TABLE I
(26 CASES)

Site	No. of Cases
Bone	7
Skin and Subcutaneous Tissue	4
Tongue	2
Nasopharynx	2
Soft Tissue	2
Spinal Cord	2
Stomach	2
Breast	1
Bronchus	1
Testis	1
Soft Palate	1
Tonsil	1

is almost as great as the "percentage loss" during the entire nine years following, as there is only a difference of 37 per cent between the one-year survival rate and the ten-year survival rate. The "survival drop" during those nine years is gradual. After the ten-year mark has been reached the "loss" from year to year is hardly significant. Thus, if a patient survives ten years without recurrence there is very little risk of a recurrence during the following twenty years. Only 8 of the 40 cases surviving ten years have died since and these had evidence of active disease prior to the ten-year mark. Craver[1] reports 22 living patients showing survival from ten to seventeen years in a series of 250 proved cases treated at Memorial Hospital. The results of the present series are comparable to the most recently reported figures of Hynes[3] in 1955.

Survival by Stage of Disease. The staging as outlined in this paper is essentially the same as in the previous paper,[5] but Stage II is divided into two subgroups A and B, according to the absence or presence of constitutional symptoms (Table III).

Jackson and Parker[4] advocate radical

TABLE II

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1954
GROSS SURVIVAL RATES
(291 CASES)

Time (yr.)	No. of Cases	Survival	
		No.	Per Cent
1	291	194	66
3	252	128	51
5	221	96	43
10	139	40	29
15	64	16	25
20	23	6	26

TABLE III

STAGING OF HODGKIN'S DISEASE
TORONTO GENERAL HOSPITAL

Stage	
I	Involvement of a Single Site or Lymphatic Region
II	Involvement of 2 or 3 Proximal Lymphatic Regions A—with no symptoms of generalized disease B—with symptoms of generalized disease
III	Involvement of 2 or More Distant Lymphatic Regions

TABLE III-A

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1954
RADICAL DISSECTION PRIOR TO ADMISSION FOR IRRADIATION
(14 CASES)

Stage I—Postoperative; no Findings on Admission—8 Cases	
No Recurrence to Date—2 cases	
Subsequent Recurrences—6 cases	
Postoperative Recurrence on Admission—6 Cases	
No Recurrence to Date—1 case	
Subsequent Recurrences—5 cases	

dissection followed by irradiation whenever the disease seems to be sharply confined to a readily accessible region. In the present series, as shown in Table III-A, there are included 8 cases of Stage I irradiated as a postoperative measure, and only 2 of these have had no recurrence to date. The 2 survivors had involvement of the tibia and nasopharynx, respectively. Also included are 6 cases following radical dissection of the initial involvement, but who had palpable evidence of disease elsewhere as well as at the operative site on admission. Only 1 of the 6 has responded well with no evidence of recurrence to date. This case developed a local recurrence within one month following a radical neck dissection at the age of four and is now well at twenty-five years of age.

Upon studying the survival rates accordto the stage of the disease, as in Table IV, one is impressed by the remarkable difference between the survival rates of Stage I and Stage III. The difference is more than 50 per cent up to the fifteen-year mark.

Influence of Symptoms of Generalized Disease on Survival Rate. The difference in the survival rates is just as dramatic when the cases are separated according to the presence or absence of symptoms of generalized disease, as in Table V. The absence of constitutional symptoms is almost as important as the staging for the purpose of assessing the prognosis. This influence is

TABLE IV

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1950
FIVE TO TWENTY YEAR SURVIVAL BY STAGE OF DISEASE
(221 CASES)

Stage	Survival							
	20 Yr.		15 Yr.		10 Yr.		5 Yr.	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
I	9	33	24	50	43	58	60	71
II	8	37	19	21	40	35	70	56
III	6	0	21	0	56	2	91	15
All Cases	23	26	64	25	139	29	221	43

not as evident at the five-year interval as later. It is gratifying to note that 42 of 136 cases (or 31 per cent) with evidence of generalized disease on admission survived five years.

Influence of Age on Survival Rate. The age of the patient has also an important influence on the prognosis. Referring to Table VI, the median age of onset is found to be a little less than forty years of age and the survival rates are definitely better up to thirty years of age, the best survival rate appearing in the twenty to thirty age group. The 6 survivals of the first decade are still alive and have been free of recurrence since the initial control by irradiation.

TABLE V

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1950
THE INFLUENCE OF SYMPTOMS OF GENERALIZED DISEASE ON FIVE AND TEN YEAR SURVIVAL
(221 CASES)

	5 Yr. Survival	10 Yr. Survival
No Symptoms Stages I and II-A	64% (85)	60% (58)
With Symptoms Stages II-B and III	31% (136)	6% (81)
All Cases	43% (221)	29% (139)

TABLE VI

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1950
THE INFLUENCE OF AGE ON FIVE YEAR SURVIVAL
(222 CASES)

Decade	No. of Cases	5 Yr. Survival	
		No.	Per Cent
0–10	11	6	55
11–20	27	14	52
21–30	48	30	62
31–40	41	18	44
41–50	33	13	39
51–60	32	11	34
61–70	21	3	14
71+	8	1	12
Total	221	96	43

Influence of Sex on Survival Rate. The influence of the sex of the patient on the five and ten-year survival rate is shown in Table VII. Although this is not as significant as the age factor, the female sex seems to have a better prognosis in spite of the fact that the disease is twice as prevalent among the male sex.

Influence of Duration of Disease Prior to Treatment on Survival Rate. The facts revealed in a study of the influence of the duration of the disease on the survival rates are very instructive, but before discussing this influence a finding should be mentioned which is of interest only as it has aroused discussion in the past. Certain patients with Hodgkin's disease have reported that the lumps first noticed by them had fluctuated in size for several months and in some instances had completely disappeared temporarily only to recur in the same site. The records of this series show that only 8 per cent or 24 patients have given this history prior to admission.

TABLE VII

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1950
THE INFLUENCE OF SEX ON FIVE AND TEN YEAR SURVIVAL
(221 CASES)

	No.	Per Cent
5 Yr. Survival		
male	141	40
female	80	50
All Cases	221	43
10 Yr. Survival		
male	85	24
female	54	37
All Cases	139	29

TABLE VIII

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1950
THE INFLUENCE OF DURATION OF DISEASE PRIOR TO TREATMENT ON FIVE YEAR SURVIVAL*
(221 CASES)

Stage	Duration		
	Under 6 Mo.	6 Mo.–2 Yr.	More than 2 Yr.
I	59%	82%	87%
II	46%	53%	83%
III	13%	11%	19%
All Cases	39% (88)	47% (79)	55% (36)

* Duration unknown 18 cases.

Much stress has been placed on early diagnosis, and from the standpoint of the response to treatment according to the stage of the disease one would agree, but from the standpoint of a complete assessment of the individual case of suspected Hodgkin's disease one would agree with reservations. Table VIII shows that the cases in which a lump of several months' duration prior to seeking medical attention is recorded have longer survivals than those seeking treatment under six months from the onset of disease. The possible exception is in the cases in Stage III which have a poor prognosis in any case.

To substantiate this finding a study was made of the 27 cases which survived more than ten years without evidence of recur-

TABLE IX

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1945
STUDY OF CASES SURVIVING MORE THAN TEN YEARS WITHOUT RECURRENCE
INFLUENCE OF DURATION OF DISEASE PRIOR TO TREATMENT ON SURVIVAL
(27 CASES)

Median Duration—12 mo.
Mean Duration —20 mo.

Duration	No. of Cases	Per Cent of Total
Under 6 Mo.	6	22
6 Mo. to 11 Mo.	5	18
12 Mo. or More	16	60

rent disease since the initial control (Table IX). In this group the median onset to treatment interval was twelve months and the average duration on admission was twenty months. Only 6 of the 27 cases were diagnosed less than six months after onset.

The combination of the two factors—(a) the stage of the disease and (b) the duration of symptoms—provides an excellent criterion of the chronicity or acuteness of the disease in any particular case. One is inclined to believe from the evidence at hand that it is extremely important to attempt to establish the rate of progression before embarking on any form of treatment, or even attempting a biopsy, provided one has ruled out the possibility of infective origin.

In most cases the chronicity of the disease can be decided on the first observation of the patient. If the rate of growth or the acuteness of the disease cannot be determined on first observation and if a lymphomatous disease is suspected, a period of observation from two to four weeks or even longer in isolated cases would not only benefit the patient but would also be of invaluable assistance to the physician directing the plan of treatment. This period of observation would require extreme tactfulness on the part of the physician in reassuring the patient, and probably would be contraindicated if the patient happened to be over-apprehensive. Any gross changes could be detected within two weeks and treatment instituted accordingly. For example, if a patient with only a Stage I lesion showed gross change within two to three weeks, that patient should receive the benefit of complete segmental irradiation. If no change could be detected in the observation period, one would be inclined to risk irradiating only the regions of the most proximal lymph nodes.

The radiotherapist is not anxious to irradiate more normal tissue than is necessary; but by segregating the Stage I cases of the entire series which received treatment to the single involved area only, and which were followed ten years, it is estimated that 65 per cent (11 of 17) of these developed recurrences within ten years. In other words, one can assume that only 35 per cent or approximately one-third of the patients diagnosed clinically as Stage I Hodgkin's disease are true Stage I cases.

Influence of Prophylactic Irradiation on the Survival Rate. A study of the value of prophylactic irradiation, either of the regions of the most proximal lymph nodes of segments of the entire main lymphatic chain, is a natural sequence to the previous discussion. Continuing to take into consideration the clinically Stage I cases followed at least ten years in this series, one finds that of 22 cases which received some form of prophylactic irradiation to uninvolved areas, there are 13 cases (or 60 per cent) which survived more than ten years without evidence of recurrent disease. One also discovers that the other 40 per cent survived much longer on an average than the Stage I cases which recurred after the initial irradiation of the involved site only.

Combining Stage I, and Stage I and Stage II-A, thus including all the cases requiring a decision regarding prophylactic irradiation, a table (Table X) was compiled which revealed the possible benefit derived from segmental irradiation beyond the clinical involvement. Allowing for the statistical

TABLE X

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1950
THE INFLUENCE OF PROPHYLACTIC IRRADIATION TO ALL PROXIMAL LYMPHATICS IN STAGES I AND II ON FIVE TO FIFTEEN YEAR SURVIVAL
(133 CASES)

	Involvement Only Treated	Involvement Plus Proximal Lymphatics Irradiated
5 Yr. Survival	46% (41)	68% (92)
10 Yr. Survival	31% (26)	53% (58)
15 Yr. Survival	26% (15)	43% (28)

error, one could estimate from this table that prophylactic irradiation increases the survival rate at least 20 per cent. It was also noted that initial prophylactic irradiation seemed to result in a prolongation of the survival of these cases which later developed recurrent disease.

Influence of Pregnancy on the Survival Rate. As a matter of interest only, a study was made to the 13 cases complicated by pregnancy either at the onset of the disease or following the initial control of the disease (Table XI). Three of these patients had pregnancies both at the onset and following the initial control. The 8 patients who were pregnant when the disease was first noted have responded to treatment somewhat better than expected. The survivals to date are listed but a few have not been observed for a period sufficiently long for adequate assessment. The twenty-five year survival, still free of disease, was mentioned earlier in this paper.

Pregnancies subsequent to the control of the disease do not seem to alter the expected survival according to the stage on admission. These results are supported by Hartvigsen[2] in a recent report on Hodgkin's disease and pregnancy.

DOSE

The course of irradiation for Stages I and II Hodgkin's disease in this center entails

TABLE XI

HODGKIN'S DISEASE ASSOCIATED WITH PREGNANCY
TORONTO GENERAL HOSPITAL
1928–1953

A. Pregnant on Admission—Survival to Date (Years)
8 Cases—25+; $11\frac{8}{12}$; 7+; $\frac{10}{12}$; $2\frac{4}{12}$; 4+ A.W.D.; 3+; 2+. (Three had subsequent pregnancies.)

B. Pregnancies Subsequent to Control of Disease
8 Cases—5+ untreated; 12+; 11; 10+; 5+; ($11\frac{8}{12}$; 7+; 2+; Included in A)

adminstering a tumor dose of 2,500 r –3,000 r in two weeks to each area of involvement, as well as a tumor dose of approximately 1,000 r to each of the proximal lymph node regions. If indicated, segmental irradiation of all the chief lymphatic chains is advised to supplement the radical treatment of the involved areas. The blood picture and general condition of the patient are closely observed and "rest periods" of one to three weeks allowed for recovery if necessary. Thus, the initial course of treatment may require two to three months.

CHEMOTHERAPY

Since 1947 the advent of the various chemotherapeutic agents has provided another weapon for the control of generalized Hodgkin's disease. Table XII demonstrates the possible influence of chemotherapeutic agents such as nitrogen mustard, triethyl-

TABLE XII

HODGKIN'S DISEASE TREATED BY IRRADIATION
TORONTO GENERAL HOSPITAL
1928–1953
THE POSSIBLE INFLUENCE OF CHEMOTHERAPY ON SURVIVAL RATE
STAGES II-B AND III
(33 CASES)

	No Chemotherapy	Chemotherapy during Course of Disease
1 Yr.	54% (137)	79% (33)
2 Yr.	42% (137)	48% (33)
5 Yr.	20% (119)	33% (21)

enemelamine, ACTH and cortisone. The authors feel that this table shows only the trend, as these agents were prescribed chiefly for the more hopeful cases of generalized Hodgkin's disease. In many instances it was prescribed for multiple recurrences after a long remission. On the other hand, a few of these cases survived one to three years on chemotherapy alone, when further irradiation would have been difficult. Consequently this comparison in tabular form was considered justifiable. According to the table, chemotherapy has chiefly aided in allowing a higher percentage to survive beyond one year, but certain isolated cases have benefited by a series of remissions of short duration at various periods during the course of the disease.

ASSOCIATED DISEASES

Brief comment only is made on the associated diseases or medical conditions most frequently encountered in this series of cases, as in Table XIII. Of those classed as "other malignancies," 2 were actually myeloid leukemia, the patients dying of this condition after four and thirteen years, respectively, and both patients had previously had no sign of recurrence since the initial control. The other cases had malignancies of various sites such as cervix, breast, rectum, skin, etc.

Three cases, all female, developed clinical signs of myxedema eight to ten years after control and all had received intensive roentgen therapy to both cervical chains. Herpes zoster seemed to be the most frequent complication and with 2 exceptions the attack of herpes zoster ushered in a series of recurrences finally resulting in terminal disease, after a comparatively long remission. The 2 exceptions had clinical evidence of herpes zoster on admission. The other conditions mentioned require no special comment.

TABLE XIII

HODGKIN'S DISEASE TREATED BY IRRADIATION
1928–1954
INCIDENCE OF ASSOCIATED DISEASES IN PRESENT SERIES
(291 CASES)

Other Malignancies—11 Cases—3 Previous to 8 Following Control		
Diabetes	— 6 cases	diagnosed later
Tuberculosis	— 6 cases	
Anterior Poliomyelitis	— 4 cases	
Myxedema (Postirradiation)	— 3 cases	
Herpes Zoster	—14 cases	

SUMMARY

A series of 291 cases of Hodgkin's disease treated in the Department of Radiotherapy, Toronto General Hospital from 1928 to 1954 has been studied with relation to five, ten, fifteen and twenty-year gross survival rates, initial sites of disease and factors determining the prognosis. The value of supplemental prophylactic irradiation has been assessed, as well as the possible prolongation of life by chemotherapeutic agents. Comments have been made on interesting complications during the course of the disease, such as pregnancy, associated diseases and metabolic disturbances.

CONCLUSIONS

The following conclusions and estimations have been drawn, which in part have been supported by other authors.

1. The cervical lymph nodes are by far the most frequently noted initial sites of the disease.
2. The stage of the disease still ranks first as an important factor in evaluating the prognosis.
3. A ten-year survival without recurrence after the initial control is necessary before one can be reasonably confident of a cure, as shown by the year-to-year drop in survival rates.
4. A significant ten-year survival by stage has now been established—Stage I—58 per cent, Stage II—35 per cent and Stage III—2 per cent, there being comparable numbers of cases in each group.
5. A history of symptoms of generalized disease is the second most significant

factor determining a poor prognosis, the ten-year survival with this history being 6 per cent as opposed to 60 per cent in the absence of such symptoms.

6. The incidence of Hodgkin's disease rises with advancing age to a peak at thirty years of age, after which it recedes, but the twenty to thirty year decade has the best survival rate.
7. The female sex, while in the minority in incidence, has at least a 10 per cent better prognosis.
8. The duration of the disease reflects the chronicity of the disease according to the stage. In general, the early cases of long duration had demonstrated longer survivals without recurrence.
9. A plea is made for deliberation and, when necessary, a period of observation before deciding on the plan of treatment. The survival rates and the incidence of recurrences reveal that there is at least a 35 per cent error in clinical staging. This fact must be borne in mind when initial treatment is planned.
10. Prophylactic irradiation of at least all proximal lymph node regions is estimated to have increased the survival rates at least 20 per cent.
11. The chemotherapeutic agents have been useful in prolonging the life of selected cases. A possible increase in the survival rates up to five years is demonstrated.
12. The complication of pregnancy, particularly following the initial control of the disease, does not appear to alter the prognosis.

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ADDENDUM

Since the reading of this paper in July, 1956, the effort to obtain exact information on points on which there was a possibility of error at the time of reading has resulted in the following changes in the survival rates presented: 5-year, 38 per cent; 10-year, 24 per cent; 15-year, 18 per cent; 20-year, 25 per cent. These changes do not affect the comparative study of influences throughout the paper.

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THE ROENTGENOGRAPHY OF MAMMARY ABSCESS AND MAMMILLARY FISTULA*

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MAMMARY abscess was studied roentgenographically with the object of placing the criteria for diagnosis of this lesion on a firmer footing and to discover, if possible, factors pertaining to the gland itself which might predispose to bacterial infection.

Our material consists of 27 cases from among 2,200 women with breast lesions roentgenographed at the Northern Division of the Albert Einstein Medical Center. Actually many more were treated at the hospitial, but acute cases usually went directly to the operating room and we had no opportunity of examining them. Of our 27 cases, only 9 were puerperal and 18 nonpuerperal.

The classification of primary breast abscesses into superficial and intramammary which has been formulated by Gunther[4] in connection with pregnancy and lactation is equally applicable to nonpuerperal cases. This grouping founded on etiology is also practical. It facilitates interpretation of the roentgenograms and has important implications with regard to treatment. We purposely omit discussion of secondary infections such as retromammary abcess as being outside the scope of this report.

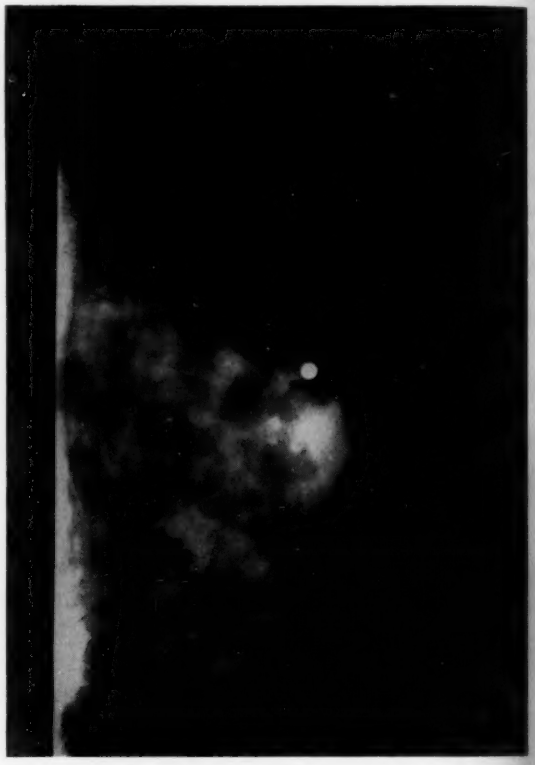

FIG. 1. *Acute superficial abscess following trauma* (*C1162*). Age twenty-two years. Tender mass in right nipple area following injury two weeks before. The abscess was pointing through the skin. Roentgenogram shows an irregular opacity impinging on thick skin.

ROENTGENOGRAPHIC CRITERIA

Our studies soon revealed that the extent and distribution of the inflammatory breast reaction could be more easily determined on the roentgenogram than by physical examination. An acute abscess appears as an irregular mass, often with flame-like extensions (Fig. 1). In the early stages and in rapidly spreading inflammation, the boundary is apt to be very indistinct. As the abscess localizes, sharp margins begin to appear and the center becomes structureless (Fig. 2). An abscess in process of encapsulation resembles a cyst, but may sometimes be differentiated by broad tentacles emerging from the margin (Fig. 3). A cyst never presents a structure of this type. Where the abscess is fairly superficial, the overlying skin and nipple may be considerably thickened and edematous, and the same is true of deep abscesses if they attain appreciable size. The sign is an important one, but may

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be absent in small deeply seated abscesses which are usually the most difficult to to diagnose. Turgescence of the superficial and deep veins is marked around acute abscesses and persists as long as infection is active. Comparison with the opposite breast will show changes in size and shape of the affected organ if the abscess is large.

An abscess which has passed into the chronic stage is often difficult to distinguish from the large cysts of mazoplasia cystica. The outlines become sharp, but if the lesion is active and the surrounding tissue is infiltrated by inflammatory cells, portions of the circumference will appear slightly blurred. In all forms of subareolar abscess the nipple will probably be edematous. It may be retracted. Vascular engorgement

Fig. 2. *Superficial abscess probably from an infected Montgomery gland* (*C1339*). Age twenty-three years. The patient noted a "pimple" on the areola ten days before. When seen, she presented a nodule 2.0 cm. in diameter surrounded by reddened skin 4.5 cm. in diameter. The roentgenogram shows a more or less circumscribed opacity under the skin of the areola. The skin is thickened.

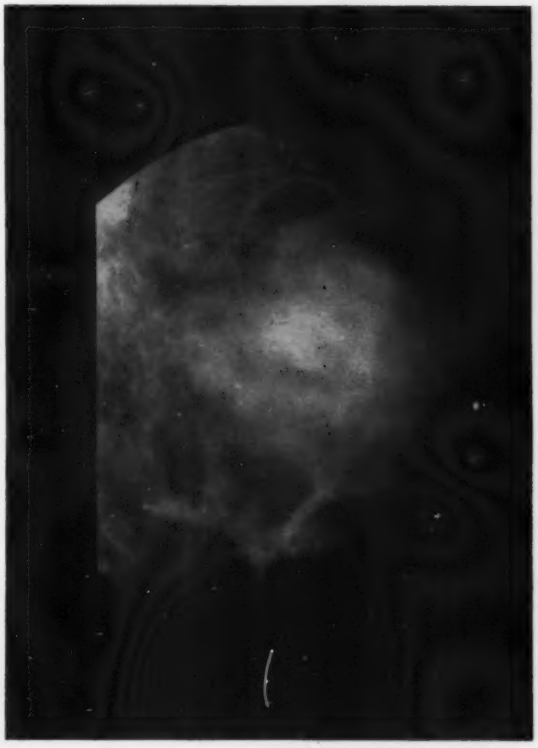

Fig. 3. *Chronic intramammary abscess* (*C778*). Age thirty-eight years. Thick whitish discharge from left nipple for one year. A mass appeared in the subareolar area six months before and increased steadily with occasional exacerbations of pain. Roentgenogram shows a very large loculated mass with a smooth edge except posteriorly where the margin is irregular. Large tentacles issue from the mass, especially at the lower edge. The tentacles are fewer than in carcinoma and are broad and rather straight. The nipple is not shown but was retracted and edematous.

is the rule. A large encapsulated abscess pushes the mammary tissue to one side. An abscess in process of healing is more difficult to discern. The lesion may be masked by fibrosis. The fibrous tissue is usually very dense. It does not follow the pattern of normal involutional fibrosis or of hyperplastic fibrosis which is the characteristic sequel of mammary dysplasia. A similar patternless fibrosis is occasionally seen in chronic abscess.

Recurrent Abscess and Mammillary Fistula

Six of our cases were recurrent; 4 had mammillary fistula. The first case which

FIG. 4. (*a*) *Mamillary fistula* (*C751*). The roentgenogram shows the nipple partly overlaid by a fold of thickened skin. The main abscess is just beneath the nipple and another abscess is seen nearby. The sinus tract was not injected with an opaque medium. (*b*) Diagrammatic drawing of Figure 4*a*: (A) abscess beneath nipple; (B) secondary abscess; (C) nipple; (D) edematous folds of skin.

drew our attention to the symptom complex, since named mammillary fistula by Atkins,[1] occurred in a nonpuerperal woman, aged forty-three years. A reddened painful mass appeared close to the areola and was opened by the surgeon. Pathologically, the lesion was characteristic of plasma cell mastitis secondary to secretory disease. The wound broke down with discharge of pus. The area was then excised and healing resulted. This time the pathologic diagnosis was abscess.

In 3 patients the original abscess arose in a distended lactiferous duct. Multiple recurrences with fistulae took place over periods ranging from several months to five years. Nipple retraction was present in some degree in the contralateral as well as in the affected breast in all 4 women.

Study of the roentgenograms of these cases revealed a retracted, sometimes edematous nipple partly surrounded by a thickened fold of skin (Fig. 4). Dilated lactiferous ducts could be traced to the fibromuscular pad. The sinus tract itself could only be rendered visible by the injection of an opaque medium.

The prodromal phase of mammillary fistula should be expected when secretory disease and abscess are seen together. Secretory disease is easily diagnosed by inspection of the film of the opposite breast in nonpuerperal women; in puerperal breasts, stagnation of milk which is the equivalent of secretory disease is hard to diagnose on the roentgenogram because

of the normal dilatation of the lactiferous ducts. Here the clinical picture can be more decisive.

Differential diagnosis of abscess on the roentgenogram alone may be difficult and sometimes impossible. Good history taking and physical examination are essential components of accurate diagnosis and, so far as roentgenography goes, are nowhere more important than in the diagnosis of mammary abscess. Without a history, abscess may be mistaken for any of the following and vice versa: inflamed secretory cyst, plasma cell mastitis, adenosis, mazoplasia cystica, fibrosis from scar tissue and carcinoma.

Inflamed cyst is an occasional complication of secretory disease.[3] Secretory disease is often asymptomatic, but nipple discharge or nipple retraction are present in some cases. Pain is usually due to chemical or plasma cell mastitis, but may be a sign of inflammation in a secretory cyst. An inflamed cyst shows perifocal edema and increased vascularity on the roentgenogram. Differential diagnosis from abscess can usually be made, but the distinction is of academic rather than practical importance; operation is indicated in any case for prevention of abscess as well as for cure of pain.

Plasma cell mastitis and abscess are easily confused. To open and drain an area of chemical mastitis is to invite infection; neglect of an abscess may result in cellulitis. The roentgen appearance of an irregularly localized mass with flame-like tentacles due to plasma cell mastitis might

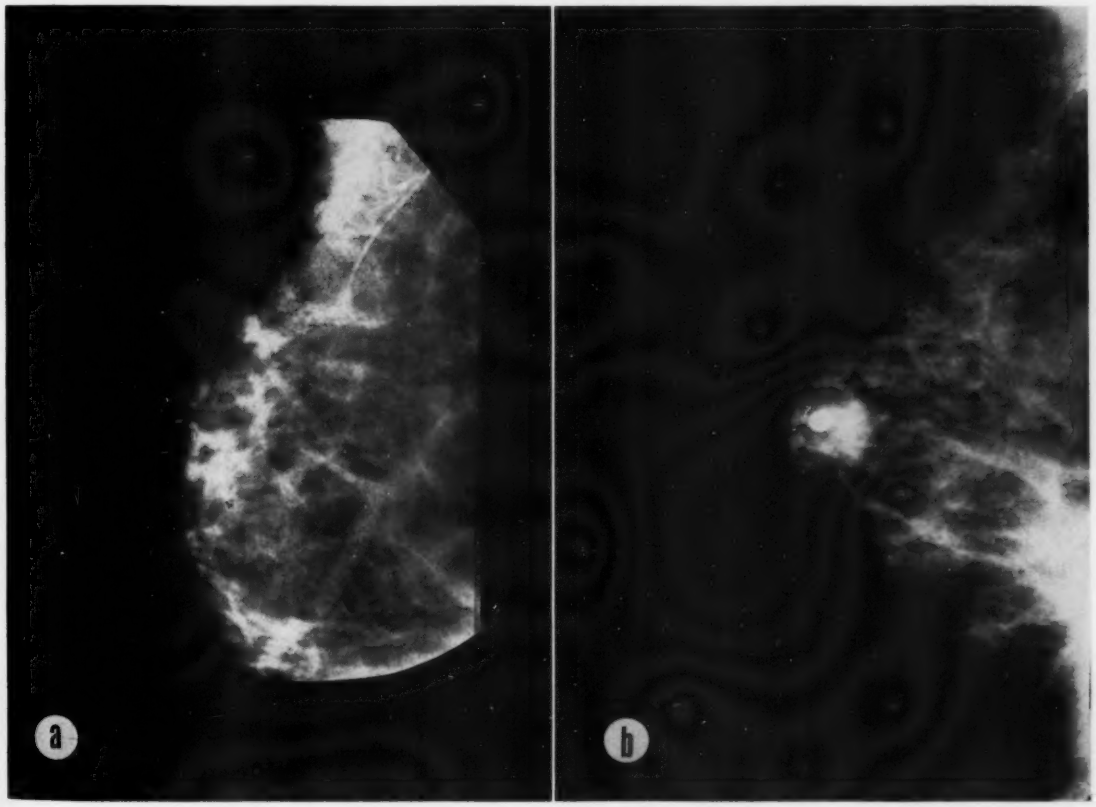

Fig. 5. *Abscess arising on basis of secretory disease with plasma cell mastitis (C270 and C1205).* Age thirty-one years. (*a*) Plasma cell mastitis was found when a secretory cyst was removed. On the roentgenogram, made after the operation, plasma cell mastitis is seen under the nipple. (*b*) Three years later, an abscess developed under the nipple at this site.

simulate abscess, but edema of the skin is not common and is never more than moderate. Absence of underlying secretory disease would exclude plasma cell mastitis. Its presence is less significant. Clinical considerations cannot be ignored. The initial fever, pain and swelling decrease in chemical mastitis; in abscess they increase in severity (Fig. 5, *A* and *B*).

Adenosis and acute abscess are often superficially alike on the roentgenogram but in adenosis the skin, although it be reddened, is thin and edema does not occur. The opacities in adenosis are nearly always bilateral and multiple. Abscess is unilateral.

Mazoplasia cystica is differentiated from chronic abscess by lack of tentacles and of edema of the skin. Fibrosis from other causes may be difficult to distinguish from healing abscess on the roentgenogram, but the history, and in most cases the presence of a scar, will determine the diagnosis.

Rarely, there is difficulty in distinguishing abscess from carcinoma. Pain and rapid onset would point to abscess, but unfortunately many patients have no idea of the duration of their tumors. Physically, most carcinomas are much harder on palpation than even a chronic abscess. On the roentgenogram abscess, as well as carcinoma, may show tentacles, although in abscess they are apt to be fewer. Distinction from inflammatory carcinoma is clinically difficult and not always easy roentgenographically. Fortunately, this challenge to diagnostic skill is seldom encountered. In the 4 cases of our series careful appraisal of the roentgenogram provided the correct answer.

DISCUSSION

Invasion of the breast by an infecting organism requires certain favorable conditions. Common causes of superficial abscesses are cracked nipple, infected Montgomery gland, etc., and are self evident. But when inflammation begins within the mammary parenchyma, some other predisposing factor must be sought. The clue to the common factor which influences the formation of intramammary abscess was suggested by our study of mammillary fistula.

Mammillary fistula has met with increasing recognition in the last few years. Five cases were described by Zuska, Crile, and Ayres[7] in 1951 under the title of "Fistulas of the Lactiferous Ducts." In all 5 "comedo mastitis" (secretory disease) was present. Only 1 was associated with pregnancy and lactation, but a swelling had existed four months before the pregnancy, and abscess did not develop until four months after delivery. The authors believe the pathogenesis of these draining sinuses to be as follows: (1) stasis of secretion, (2) dilatation of lactiferous ducts and (3) ulceration of ductal epithelium with abscess formation and rupture of the abscess to form a draining sinus. Kilgore and Fleming[6] reviewed 64 cases of recurring abscess in the areolar area and emphasized the necessity of excising the affected duct. Atkins[1] analyzed 28 cases. Twenty-five were married, only 7 were associated with pregnancy or lactation. Inversion of one or both nipples was present in 19 cases. Of our 4 cases, 2 were nonpuerperal, 1 dated five years and the other three years from a puerperium.

The reasons for the more common development of abscess from secretory disease in the subareolar area seem to be twofold: (1) a superficial focus of plasma cell mastitis is easily mistaken for abscess and if opened infection would almost certainly follow; (2) the superficial location of the affected lactiferous duct renders it vulnerable to invasion by bacteria from the skin. Caswell and Burnett[2] in a report of 6 cases call attention to this factor. In all 6 women the nipples were inverted and infection appeared to originate "on the basis of maceration and cellulitis involving the cutaneous and glandular structures in the groove of the inversion of the nipple."

Hitherto, although plasma cell mastitis and fat necrosis are of frequent occurrence, we had thought of abscess as a rare complication in secretory disease. Actually, inflamed secretory cysts are not uncommon

although they are seldom diagnosed as such. A review of our material emphasized the difficulty of distinguishing between bacterial inflammation and "chemical" or plasma cell mastitis. Several cases in which the pathologic picture was equivocal were excluded from our series, but the existence of borderline lesions suggests that secretory disease is more often the precursor of abscess in nonpuerperal women than is usually thought.

The majority of intramammary abscesses occur during the puerperium. Recently, Gunther[4] has brought forward convincing evidence that puerperal mastitis is due to retention of milk. If stagnation is present and the breast is not emptied, bacterial infection is liable to supervene some two days later.

Stagnation of secretion, whether puerperal or nonpuerperal would therefore seem the chief predisposing factor in the development of intramammary abscess. Stagnation may be expected to occur if nipple retraction or any other condition is present to prevent the free flow of milk. In nonpuerperal breasts stagnation of milk-like secretion is characteristic of secretory disease. The resultant fibrosis in the subareolar area is often associated with nipple retraction.

Two ways of checking this concept were open to us. The first was to search the breast tissue removed at operation for characteristic ducts filled with colostrum-like cells and lined by secretory epithelium. Many cases, however, especially those treated by incision and drainage, could provide no such evidence. We therefore resorted to the second and far more reliable method which depended on the roentgenogram.

Examination of the contralateral breast is an essential part of any roentgen study. Unless the two breasts are compared, important lesions may be missed and a wrong interpretation may be given of the abnormalities that are detected. In the case of abscess, for example, the possibility of secretory disease must be considered. The two may coexist and often the dilatation of ducts due to secretory disease will be masked by the abscess. But secretory disease is practically always bilateral and careful examination of the contralateral breast will reveal its presence. Similarly retraction of the nipple is often bilateral and minor degrees of this deformity are more readily appreciable on the roentgenogram than clinically. Apparent retraction is common in abscess because of edema of the surrounding tissues. It may not be possible to decide whether retraction preceded the abscess or vice versa. But if there is retraction of the contralateral nipple, it is fairly safe to say that the nipple of the affected breast was abnormal before the abscess started.

Following evaluation of alterations in the affected mammary gland, the contralateral breast was re-studied. Roentgenograms from 12 nonpuerperal cases of intramammary abscess revealed secretory disease in 10, 4 of whom had nipple retraction. Retracted nipple without secretory disease was found in the remaining 2 patients of this group. Of 7 puerperal cases, 3 had nipple retraction. In contrast were 4 superficial abscesses due to cracked nipple, infected Montgomery gland, skin infection and trauma. In all 4 the contralateral breast was normal.

Our findings taken in conjunction with the observations of others point to the conclusion that intrammary abscess rarely occurs unless a predisposing cause is present in the breast. The fact that most cases arise during the puerperium or are associated with the pathologic counterpart of lactation—secretory disease—points to stagnation of secretion as the chief precursor of bacterial infection. Treatment directed to the elimination of stasis has been shown to prevent puerperal abscess.[4] In this form of preventive medicine the roentgen examination can play an important part.

SUMMARY

Twenty-seven cases of mammary abscess in which roentgenographic studies of the breast were available are analyzed.

Primary abscess, whether puerperal or nonpuerperal, is classified as superficial or intramammary. On the roentgenogram, abscess is characterized by an opacity, irregular and poorly defined at first, more sharply outlined later. Marked edematous thickening of the skin and venous turgescence are important secondary criteria. A chronic abscess may present a few broad tentacles emerging from smooth margins.

Among 6 recurrent abscesses were 4 cases of mammillary fistula. Roentgen examination permits identification of the underlying pathology before fistula has occurred. Appropriate surgical measures may then be taken to avoid this complication.

Abscess must be differentiated from secretory disease, plasma cell mastitis, adenosis, mazoplasia cystica, fibrosis from scar tissue and carcinoma. Diagnosis by means of the roentgenogram alone is difficult and sometimes impossible. Interpretation must be made in the light of the history and physical examination.

Study of the unaffected contralateral breast reveals predisposing causes of abscess. Four cases of superficial abscess showed no abnormality of the contralateral breast. Skin or Montgomery gland inflammations were the sources of infection.

In 12 nonpuerperal women with intramammary abscess, secretory disease or retracted nipple or both were found in the contralateral breast. Of 7 puerperal cases, 3 had nipple retraction. The conclusion is drawn that stasis of secretion is the principal etiologic factor in intramammary abscess.

Roentgenography, by exposing conditions which predispose to abscess, enables the selection of suitable therapeutic measures and in mammillary fistula ensures the proper surgical approach.

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Vol. 79, No. 1

A RADIOISOTOPE METHOD OF VISUALIZATION OF BLOOD POOLS*

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UNTIL 1931 the visualization of blood pools in the body was unsuccessful. Forssman, in that year, was able to observe the right side of the heart by introducing a catheter into the right atrium of dogs and injecting radiopaque material through this catheter. In 1937, Robb and Steinberg[5] produced the first reliable roentgen visualization of cardiac chambers by angiocardiography. Apparently Nuvoli, in the year before, was able to perform successful roentgen aortography in man. Since then angiocardiography has become a very satisfactory technique for the study of blood pools in the heart and greater vessels.

With the development and extension of radioisotope scanning techniques, it appeared to be of considerable interest to extend these methods to the study of blood pools within the body and to determine whether the size, shape, and position can be adequately visualized.

MATERIAL AND TECHNIQUE

In our effort to utilize the radioisotope technique to obtain graphic illustration of the blood pools in the body, various considerations were given to different materials which could be tagged with a suitable isotope and introduced into the circulation without untoward effect to the patient. Radioactive human serum albumin tagged with I^{131} appears to be the material of choice at present. It has been used extensively in other investigations for the study of peripheral vascular disease, blood volume determinations and cardiac output without any toxic effects. In addition, serum albumin tagged with radioactive I^{131} exhibits sufficient stability in the circulation so as to insure a satisfactory scanning source. Since I^{131} tagged human serum albumin gradually releases the radioactive iodine, Lugol's solution should be given to the patient twenty-four hours before administration and should be continued for a week. Under these circumstances the amount of I^{131} taken up by the thyroid will be negligible.

Since the problem of visualizing the configuration of body blood pools is similar to our previously reported investigation of liver scanning,[1,2,4] the same general equipment and specifications have been utilized. For this work a cylindric collimator of one-half inch diameter and three inch depth was again used in conjunction with a one-half inch diameter and one-half inch thick sodium iodide (thallium activated) crystal. Scattered radiation was eliminated by thin lead filters or by integral pulse height discrimination. Sufficient lead shielding was placed around the crystal to reduce the cosmic radiation background to about 20 counts per minute. The usual x-axis scanning speed selected was ten inches per minute with about ten lines per inch recorded along the y-axis.

In order to increase the contrast in these scanograms, a counting rate cut-off circuit has been used throughout.[2] This circuit enables the operator to select an arbitrary counting rate which must be exceeded before the scan is recorded. In most of these scanning procedures, two or more simultaneous recordings were made with slightly differing cut-off levels so as to insure both maximum contrast and to avoid excessively high settings that would lose detail. In this connection a monitoring counting rate meter was used throughout both as an aid in selecting the correct counting rate level setting as well as selecting the optimum scaling factors and scanning speeds.

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Besides recording on electrosensitive Teledeltos paper, simultaneous records have also been made by incorporation of an oscilloscope-lens system for film exposure. This technique is essentially one of substituting a modulated light pulse on an oscilloscopic screen for the conventional dot recording. Each impulse is fed directly into the z-axis of the oscilloscope so that at high counting rates these dots may overlap and by such superimposition will in some cases approximate a solid scan. The dot size is considerably larger than the Teledeltos recording and may be adjusted from scan to scan. Complete details of this system are to be reported elsewhere.[3]

METHODS

To obtain the cardioscan, the patient was placed on an adjustable operating table in supine position, and 300–400 μc of I^{131} tagged human serum albumin given intravenously according to the weight of the patient. A delay of ten minutes must be observed for mixing of I^{131} tagged human serum albumin with the blood.

As the tagged albumin mixes with the circulating blood, the radioactivity over the heart increases as compared to surrounding lungs because of the larger blood pool. The cardiac area was then scanned by bringing the tip of the collimator of the scintillation counter into close proximity of the anterior chest wall in such a way that there would not be any interference with the sweep of the tube by the ribs and clavicles.

Trial runs should be made from the right fourth intercostal space in the midclavicular line to the anterior axillary line on the left side, and from the proximal end of the left clavicle to the lower costal margin on the same side in order to determine the approximate border of the cardiac blood mass. This is also necessary for adjusting the background discriminator cut-off, and for proper selection of oscilloscope light intensity and counting rate. After the proper adjustments are made in the scanner, background discriminator, scaler, and oscilloscope, the scanning procedure starts from the suprasternal notch and usually takes between twenty-five and forty minutes.

While the same general method for the scanning of aneurysms of the thoracic aorta is observed as for cardiac scanning, some modification in technique is required for scanning of aneurysms of the abdominal aorta. In this case the patient is placed in a supine position on the previously described adjustable operating table. The same amount of tagged serum albumin is given to the patient as in the cardiac scanning. After an appropriate delay for mixing of the albumin with the blood, the aneurysm is scanned by bringing the tip of the collimator into close proximity with the abdomen in the midline. A trial run is made across the hypogastric umbilical, and epigastric region and across the abdomen over the aorta. The borders of the aneurysm are determined by observation of the counting rate meter. The proper adjustments of the scaler, scanner, background cut-off discriminator and oscilloscope are then made.

CLINICAL STUDIES

In order to determine the appearance of unusual blood pools within the heart, a group of patients with normal cardiovascular systems was studied. It was found, with our techniques and equipment, that good graphic illustration of the cardiac blood pool was possible with a dose of 300–400 μc of I^{131} tagged human serum albumin. It may be observed that the size and configuration of the cardiac blood pool can now be readily compared with the cardiac silhouette on conventional roentgen studies of the chest. Separation of different cardiac chambers is not possible normally and the blood pools of the great vessels merge with the blood mass of the cardiac chambers. The border of the cardiac blood pool is not sharp for a variety of reasons. These are in part due to various motions of the heart and to respiration. Also, the resolution under this condition is probably not better than 1 cm.

It became obvious that visualization of the size and configuration of vascular pools

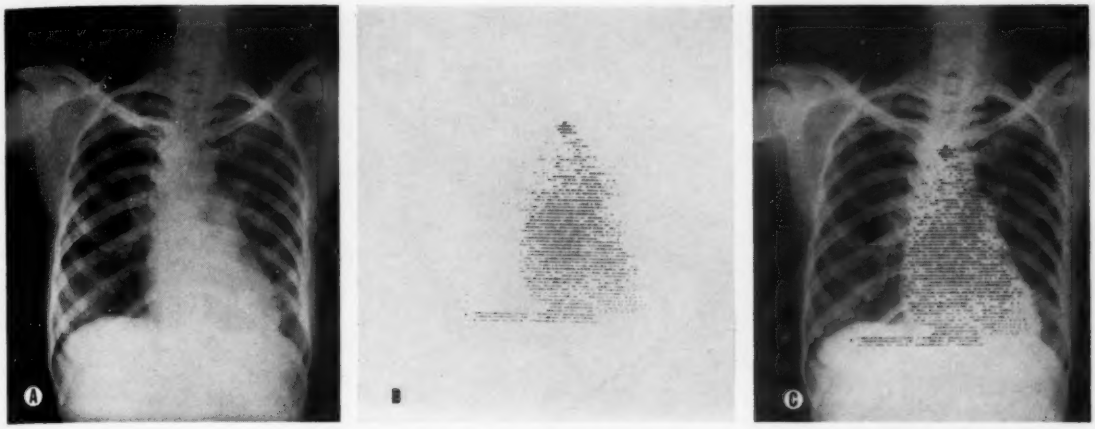

Fig. 1. (*A*) Posteroanterior roentgenogram of the chest, normal patient. (*B*) Scan of normal cardiac pool. (*C*) Superimposition of cardiac blood pool on posteroanterior roentgenogram of the chest. Note extension of cardiac blood pool to the blood pool of the liver.

would permit us to make certain observations which might be effectively applied to cardiac problems. It was possible by matching the size of the blood pool on the scanogram with the size of the cardiac silhouette on the roentgenogram to make useful clinical contributions. This technique is illustrated in Figure 1 which shows a normal cardioscan and the method of superimposition on the posteroanterior roentgenogram of the thorax.

In Figure 2*A*, an unusually large cardiac silhouette is demonstrated on the roentgenogram. The cardioscan (Fig. 2*B*) in turn shows an extremely large blood pool. This would indicate that the enlargement is primarily due to dilatation and helps to eliminate other conditions which might

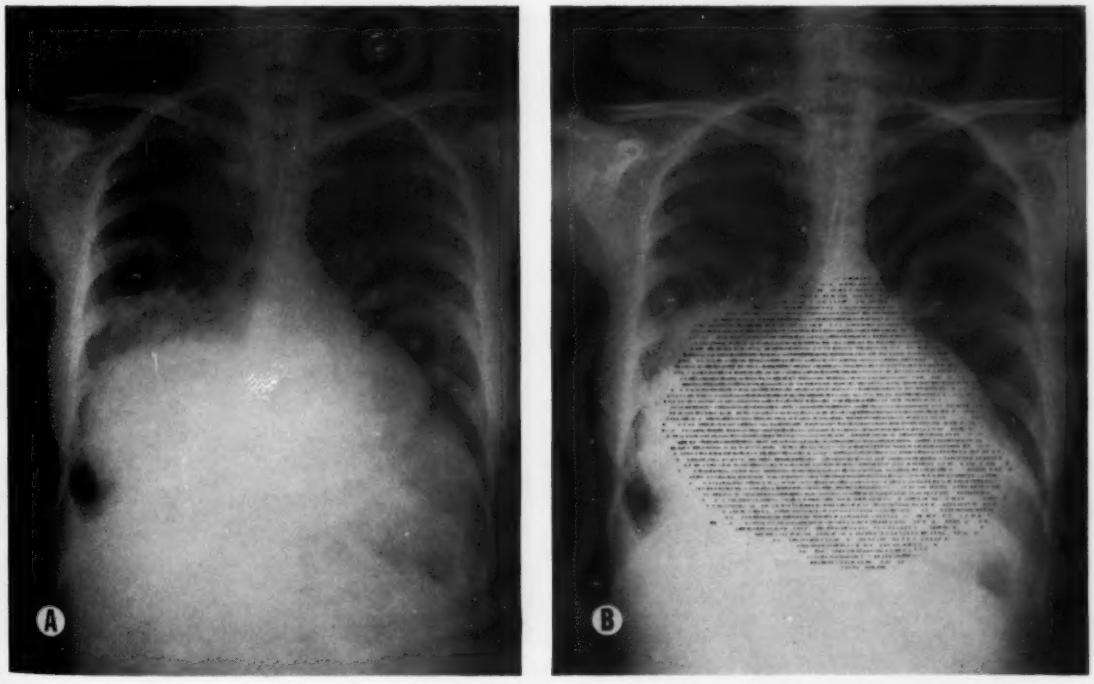

Fig. 2. (*A*) Posteroanterior roentgenogram of the chest showing enlarged cardiac silhouette. (*B*) Enlarged cardiac blood pool, shown superimposed on cardiac silhouette indicating cardiac dilatation.

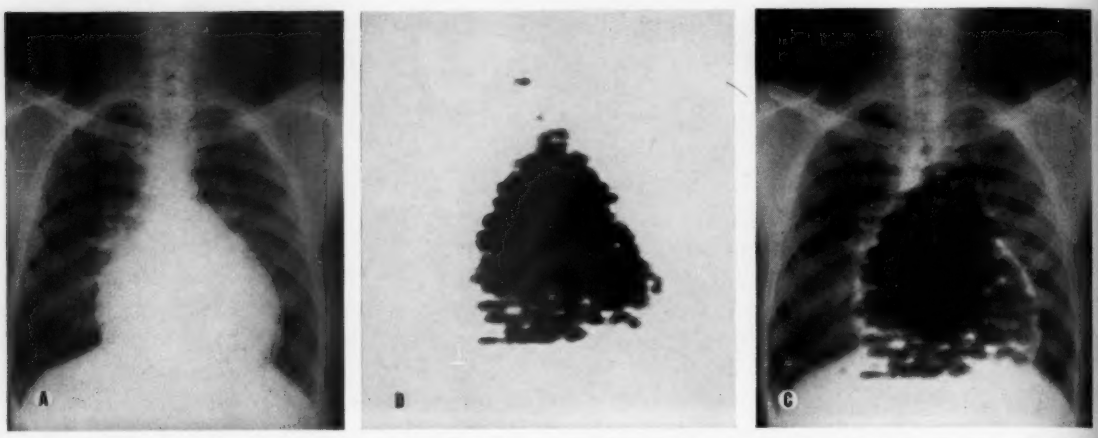

FIG. 3. (*A*) Posteroanterior roentgenogram of the chest showing enlarged cardiac silhouette. (*B*) Oscilloscopic light scan of the enlarged cardiac blood pool. (*C*) Superimposition of cardioscan on posteroanterior roentgenogram of the chest revealing cardiac enlargement and hypertrophy.

cause an increase in the size of the cardiac silhouette.

Figure 3 shows another comparison between the roentgenogram and the scanogram. Again matching of the cardiac blood pool on the cardiogram with the cardiac silhouette showed no serious discrepancy and enabled us to rule out a suspected pericardial effusion. (There is probably some hypertrophy of the left ventricle which might explain the slight difference between the left edge of the cardioscan and the left heart border.)

Figure 4 represents another cardioscan superimposed upon a roentgenogram of the thorax. As may be clearly seen, there is a

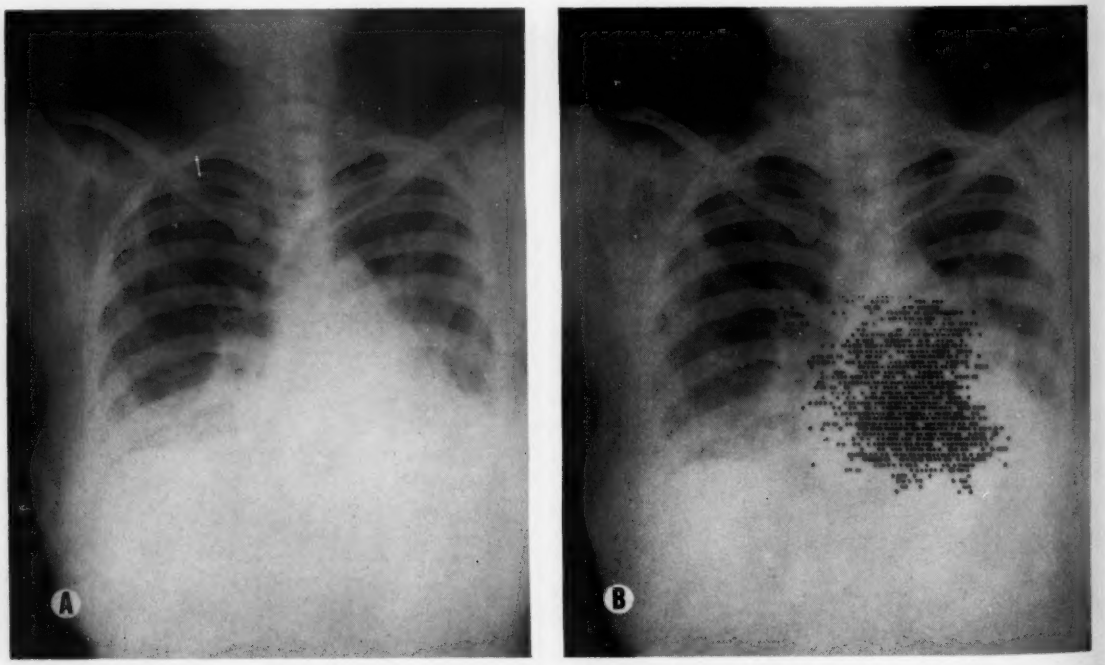

FIG. 4. (*A*) Posteroanterior roentgenogram of the chest of a patient with enlarged cardiac silhouette. (*B*) Superimposition of cardiac blood pool on posteroanterior roentgenogram of the chest indicating marked discrepancy between cardiac silhouette and blood pool.

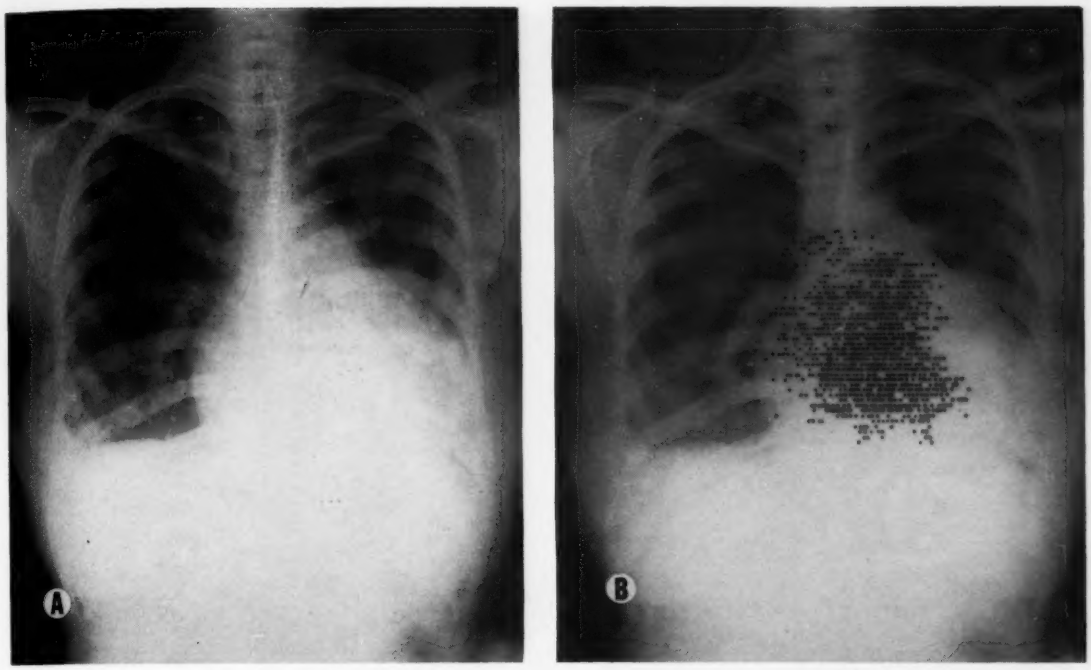

Fig. 5. (*A*) Posteroanterior roentgenogram of the chest of the patient in Figure 4 after a 500 cc. pericardial effusion was removed from the pericardial sac. (*B*) Superimposition of the cardiac blood pool on posteroanterior roentgenogram of the chest following removal of pericardial effusion. Note minor discrepancy remaining.

very marked discrepancy between the size of the heart shadow and the size of the blood pool. This strongly suggested the possibility of an effusion in the pericardial sac and subsequently 500 ml. of pericardial fluid were aspirated. The relationship between the cardioscan and the roentgenogram following pericardial aspiration in this patient is shown in Figure 5. The discrepancy has been markedly reduced although there appears to be a small amount of pericardial fluid remaining.

The roentgenogram of a patient with an unusual prominence of the right border of the cardiac shadow is shown in Figure 6*A*. Since this patient had had a mitral commissurotomy several days previously, it was considered possible that this prominence might represent an unusual clot in the pericardial cavity proper. The cardioscan superimposed upon the cardiac silhouette shows a rather marked discrepancy between the border of the blood pool and the outermost margin of the cardiac silhouette on the right side. Although no conclusive evidence was available that this truly represented an unusual accumulation of blood in the pericardial sac, it is significant to note that on a subsequent film, and superimposition of the cardioscan (Fig. 6*B*) the unusual prominence of the right cardiac border has disappeared.

Figure 7 shows the cardioscan of a patient who had recently suffered a severe myocardial infarct. A large defect is present in the inferior aspect of the cardiac blood pool. It is interesting to speculate that this defect may represent a mural thrombus since its position is consistent with the area of infarct shown in the electrocardiogram.

In addition to examining the blood pools within the heart we were also very much interested in the usual appearance which might result from aneurysms in any of the large vessels. A number of patients who presented roentgenograms indicating aortic aneurysms were studied. An effort was

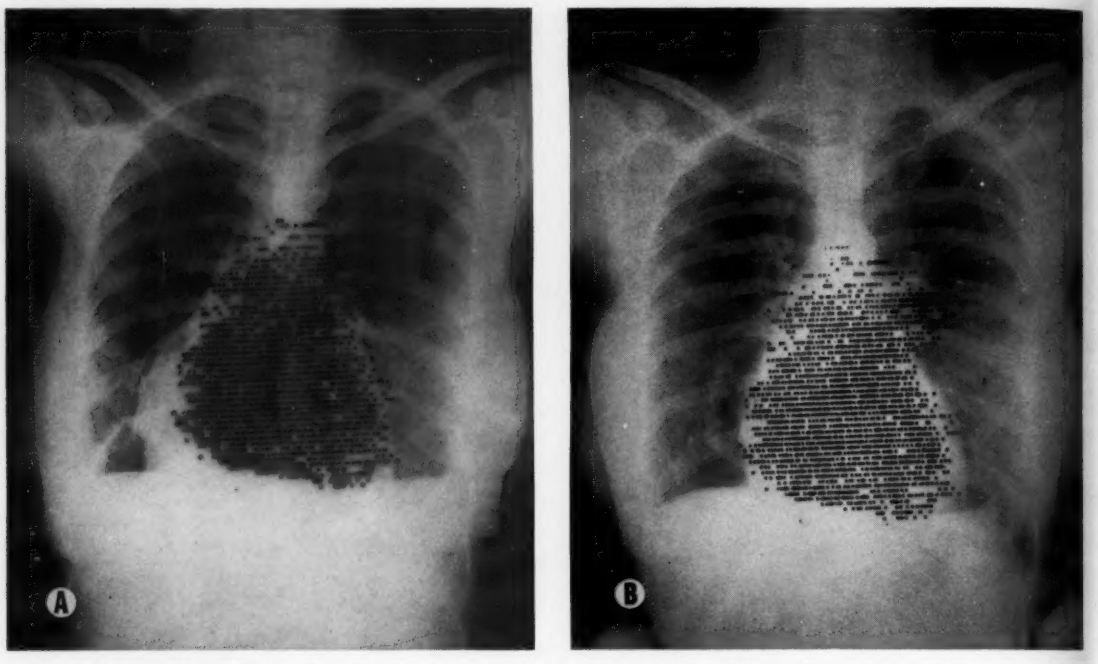

FIG. 6. (*A*) Superimposition of cardioscan on posteroanterior roentgenogram of the chest of a patient after mitral commissurotomy. Note abnormal right cardiac border thought to be enlarged pericardial sac on the right side. (*B*) Superimposition of cardioscan on posteroanterior roentgenogram of the chest taken seventy-five days later. Note disappearance of unusual right cardiac border and no evidence of discrepancy between cardiac shadow and cardiac blood pool. (By permission of *The Journal of Applied Radiation and Isotopes*, Pergamon Press Inc.)

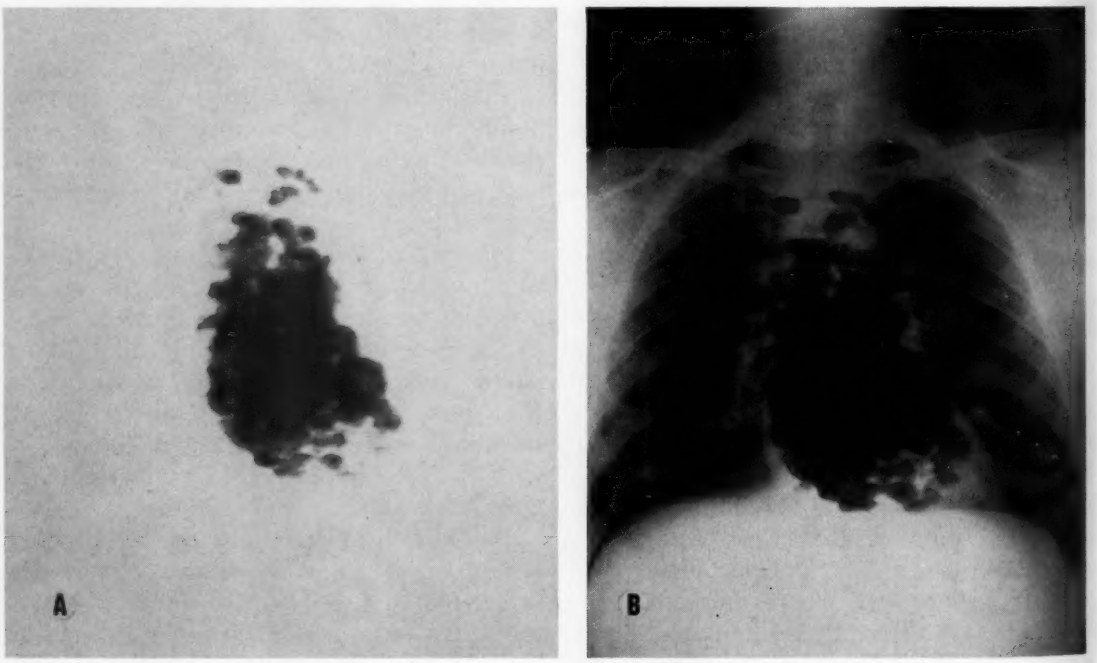

FIG. 7. (*A*) Oscilloscopic cardioscan revealing defect in the inferior aspect of cardiac blood pool of patient with recent myocardial infarct. (*B*) Cardiac blood pool superimposed on posteroanterior roentgenogram of the chest.

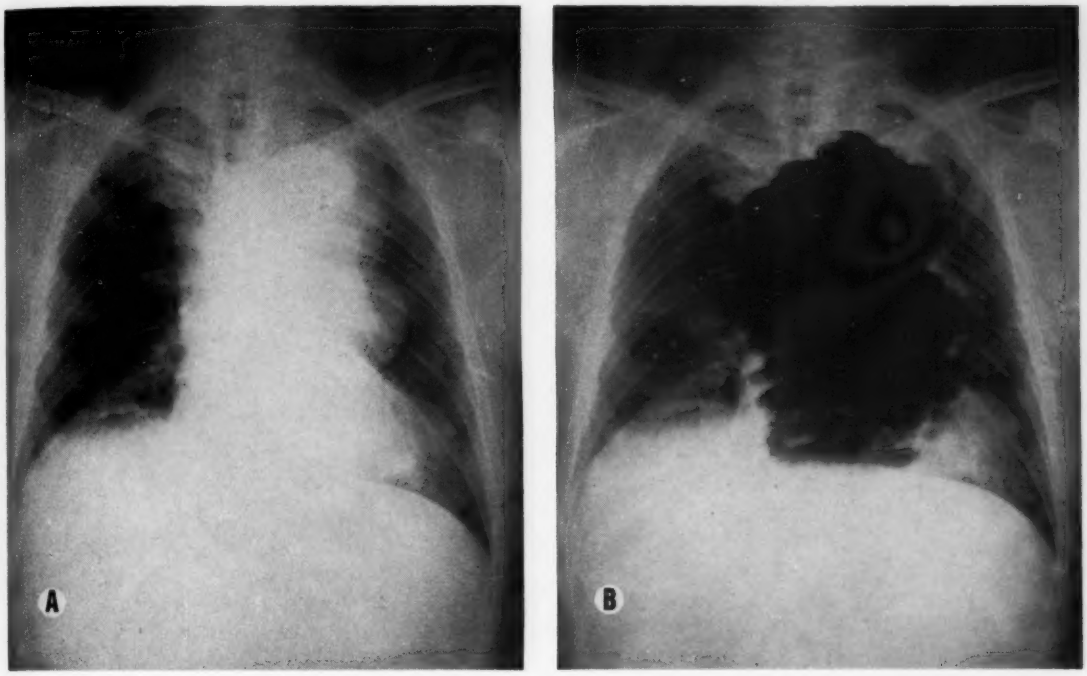

FIG. 8. (*A*) Posteroanterior roentgenogram of the chest showing widening of mediastinum. (*B*) Cardioscan of this patient superimposed on posteroanterior roentgenogram of the chest showing large blood pool above cardiac blood pool which corresponds favorably with mediastinal mass proving aneurysm of the aorta.

made to determine whether these blood pools could be clearly visualized and whether they coincided with the changes observed roentgenographically. The method is essentially similar to that used for study of the heart and has been described previously.

Figure 8*A* represents a patient with marked cardiac enlargement and unusual widening of the mediastinum which is known to be due to aneurysm of the aorta. Figure 8*B* shows the cardioscan of this patient as superimposed upon the roentgenogram. An unusually large blood pool is clearly visualized which corresponds very favorably with the roentgenographic demonstration of the aortic aneurysm. It is believed that this method can differentiate aneurysm of the aorta from masses in the mediastinum and serves much the same purpose as angiocardiography. However, scanography is simple and without hazard.

We were also able to obtain patients in whom aneurysms of the abdominal aorta were present, and in Figures 9 and 10 a comparison between the roentgenograms, aortograms and the scanograms is shown. Again the blood pools which are seen on the scanogram correspond very favorably with the blood pool visualization on the aortogram.

DISCUSSION

The application of the radioisotope scanning methods to visualization of blood pools is a relatively simple technique and is without hazard. It would appear to be very useful in many situations where angiocardiography and aortography might be helpful. It should be emphasized that although fairly sharp delineations may be obtained on our scanograms, visualization of the blood pools by angiocardiography, by the very nature of the process, is much sharper and superior in detail. Whenever fine detail is essential, angiocardiography is, therefore, of distinct advantage. Although our investigations have just begun to touch upon the various conditions in which scanograms of the cardiac and vascular pools might be

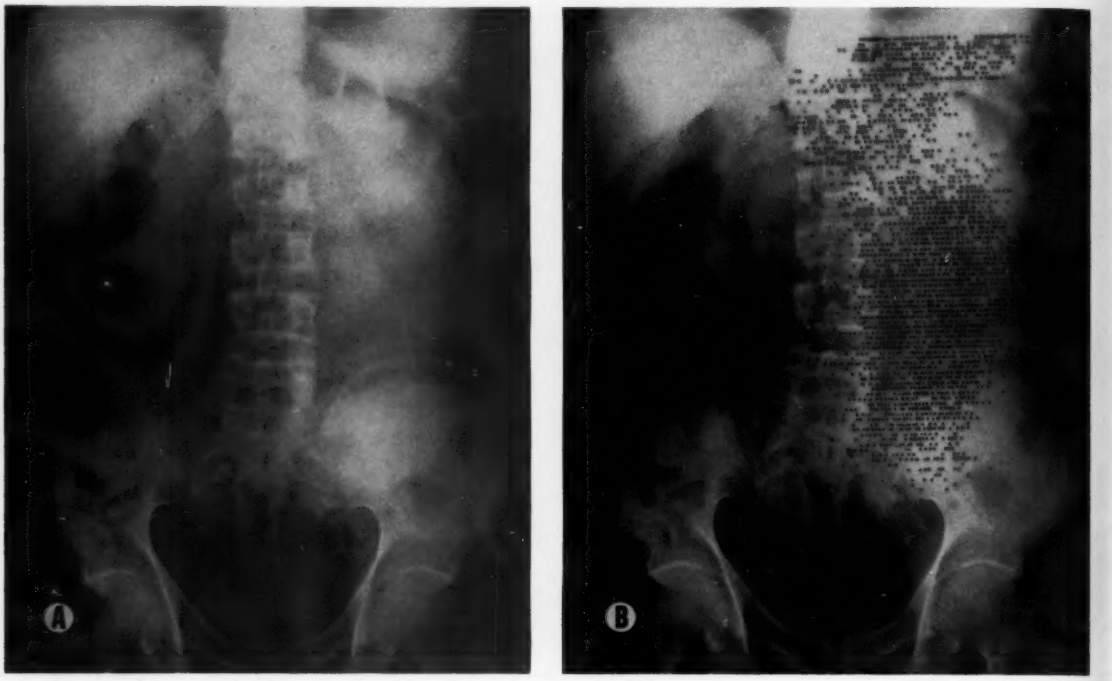

FIG. 9. (*A*) Flat roentgenogram of the abdomen showing soft tissue shadow overlaying the left psoas shadow (*B*) Superimposition of the scanogram of the abdomen on flat roentgenogram of the abdomen showing large blood pool.

useful, there is most encouraging evidence that this can be an effective adjunct in the study of various cardiac and vascular problems. These would include such conditions as pericardial effusions, aneurysms of the thoracic and abdominal aorta, differentiation of aneurysms of the aorta from mediastinal and abdominal masses, and the possible visualization of neoplasms and thrombi of the cardiac wall which might encroach upon the blood pools.

Since the beginning of these studies we

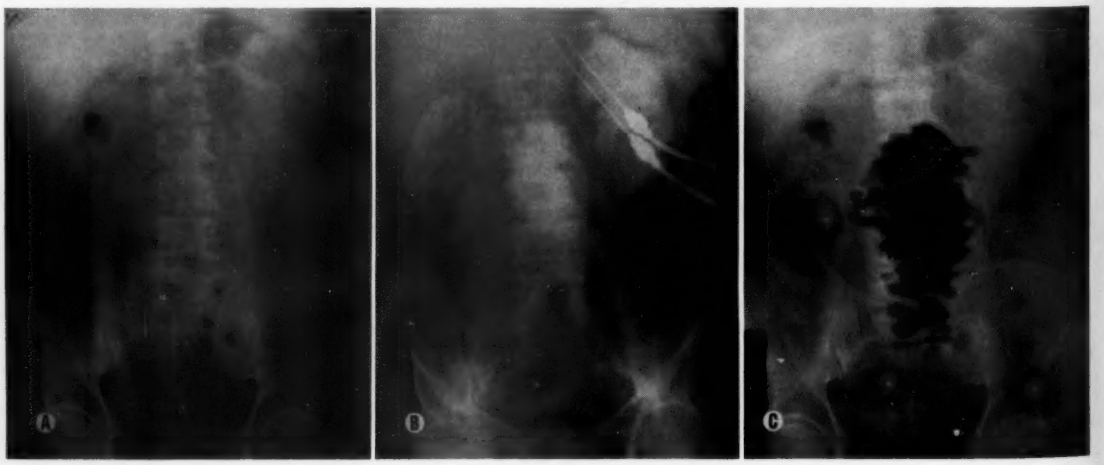

FIG. 10. (*A*) Flat roentgenogram of the abdomen. (*B*) Aortogram, showing large blood pool. (*C*) Superimposition of scannogram on flat roentgenogram of the abdomen showing correspondence of blood pool with pool shown in aortogram.

have made gradual improvements in the scanning techniques and equipment. It appears readily possible to make continued improvement which would be manifested in clearer delineation of the blood masses. Consideration is also being given to radioactive compounds or radio-elements which might have shorter biologic half life, thus permitting larger initial doses and making it possible to further improve the delineation. For example, protein tagged with I^{132} would immediately permit a much larger initial dose.

It should be pointed out that very careful attention must be given to the effective counting rate which is being measured and the differential between the radiation arising from the pools to be studied and the surrounding structures. This will determine the setting for the cut-off circuit and will have considerable influence on the delineation of the blood pool. While the techniques described in this paper have proved satisfactory with our scanning device and have given us useful results, successful attempts to perform similar studies with other equipment will require a clear understanding of the scanning method and careful attention to the radiation differential from the blood pools and surrounding structures.

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TRAINING PROGRAMS IN CLINICAL USE OF RADIOACTIVE ISOTOPES*

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THE demand for physicians to direct radioisotope programs is continually increasing. The Atomic Energy Commission has established definite training criteria for licensure for various isotope procedures, and for many people the question arises of where to obtain this training. The American Board of Radiology is now examining in nuclear medicine, and while their standards have not yet been explicitly set forth, it is evident that radiologists will be looking for courses on isotopes.

The purpose of the present study was to determine what courses are available, what sort of needs they fill, and how many people they can take care of. Before going into detail regarding them, perhaps we should review the sort of material they are supposed to cover.

The Atomic Energy Act of 1954 places upon the Atomic Energy Commission the responsibility for safe use of "by-product material" or radioactive isotopes. The Commission in turn delegates this authority to the Isotopes Extension of the Division of Civilian Application. Safety is in general interpreted within the framework of the recommendations of national and internal bodies, concerned with such problems, for exposure to the user or to the casual bystander. When administration to human beings for therapy, diagnosis, or research is concerned, the physician-patient relationship also comes under consideration. For general safety problems, the Division of Civilian Application has established an Advisory Committee on Isotope Distribution, with a Sub-Committee on Human Applications. It is the function of this sub-committee to try to make sure that no human being receives too large a dose of radioactive material. To this end they have tried to establish reasonable dosage ranges for therapy and for diagnostic tests, and to make sure that doses in normal individuals used as controls in research projects should be kept very low. They have therefore outlined the minimum training and experience requirements considered necessary to ensure safety for various types of isotope use. Applicants have been required to show evidence of this training before receiving licenses to obtain radioactive isotopes. While there have been scattered complaints that the AEC is acting to restrict the practice of medicine by these requirements, there has been much more widely expressed gratification over reasonable control of potentially dangerous drugs.

Requirements are divided into "basic radioisotope training" and "active clinical participation." The first comprises principles and practice of health safety, familiarity with radiation measuring instruments and techniques, mathematics required for the necessary calculations, some actual experience handling isotopes, and some information as to the biologic effects of radiation. This can be obtained by lectures, reading, and basic laboratory experiments. Active clinical participation includes examination of patients to determine suitability for the procedure proposed, actual carrying out of the procedure in enough cases to give confidence, and a long enough period of training and experience to permit of adequate patient follow-up where this is desirable. Obviously, this can be obtained only in connection with a clinical group.

No definite plan or outline for the basic course has been presented, but naturally various academic courses would be acceptable. That obtained in a brief preceptor-type relationship with an isotope service is

* Presented at the Thirty-ninth Annual Meeting of the American Radium Society, Quebec City, Quebec, Canada, May 29–June 1, 1957.

likely to be borderline, and may be quite inadequate. On the clinical side, however, explicit data as to required experience are listed for each type of use. These are not rigid criteria; within a certain framework substitutions may be made. It is the overall picture that is important. The simplest requirement is for the person who wants to do only diagnostic radioiodine studies of thyroid function—basic radioisotope training *plus* thirty hours of active clinical participation, with 10 thyroid uptakes. It is sometimes assumed that the thirty hours includes the basic training, but this should be considered insufficient. Wide qualification for many uses calls for at least one hundred hours of training, with experience in a variety of procedures.

At least 100 colleges and universities offer courses that would satisfy the basic training requirement, but courses in clinical applications are much harder to find. With the aid of files of the Atomic Energy Commission and of the American Board of Radiology, in addition to various personal contacts, I was able to find only 26 institutions in the United States giving courses open to others besides their own residents. To be sure, in many hospitals it is possible for at least some of the residents to obtain at least some isotope experience. It is also possible for some physicians to obtain preceptor-type training in hospitals.

The directors of the courses in the 26 institutions were most cooperative in givng outlines of study and other details such as enrollments, fees, and their ideas as to the type of licensure the courses should lead to. I am deeply indebted to them for their courtesy.

Courses last from four days to nine months; enrollments vary from 1 to 40, fees from nothing to $700.00. The total annual enrollment in all of them would be less than 500 students, and of these at least one-third would be in courses of two weeks or less.

Most of the directors of the short courses felt that their students should be qualified to do some diagnostic procedures, one or two felt that the courses served only as basic orientation, and two felt that their graduates should be able to do all standard procedures. Directors of courses totalling one hundred hours or more felt that their graduates should be ready for all standard procedures, but most of them stated that they based individual recommendations on individual performance in laboratory and

TABLE I

COURSES NOT EXCEEDING TWO WEEKS

Location	Time Spent	Number Enrolled	No. of Laboratory Periods	Final Examination	Fee	No. of Times Given/Year	Authorization Expected
South Dakota	4 da.	10	4	No	$5	2	Diag. I, Blood Vol.
Washington, D. C.	1 wk.	15	4	Yes	$125	1	Diag. I, possibly P Ther.
Michigan	1 wk.	2	?	No	?	At need	Diagnostic procedures
Ohio	6 da.	40	4	Yes	$30 or $60*	1	Basic only
Ohio	2 wk.	10	12(?)	Yes	$60 or $120*	1	Diag. and Ther. I and P.
Illinois	1 or 2 wk.	12	Several	?	$200	1	Diag. I; possibly P and Au†
Colorado	1 or 2 wk.	2	?	No	$50	Irregular	Possibly Diag. I
Indiana	2 wk.	30	6	Yes	$100	Biennial	All usual uses
Washington, D. C.	1 afternoon/wk. 10 wk.	25	4	Yes	$20	2	Various diagnostic; P Ther.
Kansas	6 2-da. sessions	10	6	?	$175	1	All usual†
Tennessee	2 wk.	4	24 hr.	?	$100	1	All usual
Maryland	6 hr./wk. 12 wk.	2	24 hr.	?	None	2	All usual†
Louisiana	5 hr./wk. 14 wk.	12	14 hr.	?	$45	1	All usual†

* Course given under auspices of American College of Physicians; lower fee for members of College.

† Students encouraged to come back to clinics and follow-ups to gain added experience.

TABLE II

LONGER COURSES FOR ONE TO THREE STUDENTS

Location	Time Spent	Number Enrolled	No. of Laboratory Periods	Final Examination	Fee	No. of Times Given/Year	Authorization Expected
Michigan	4 wk.	2	Clinical	No	Not stated	Start any month	All, with Isotope Commission
Michigan	8 wk.	2	Clinical	No	Not stated	Start any month	All, private practice
Michigan	3 mo.	1–3	Many	No	None	Start any time	All usual
California	1 mo.	3	Basic	Yes	$250	6	Basic only
California	1 or 2 mo.	1	Clinical		$250 per mo.	6	All usual
Massachusetts	2 da./wk. for 3 mo.	2	Many	No	None	4	All usual
New York	4 afternoons/wk. for 3 mo.	2	Clinical	No	$300	3	All for iodine
Tennessee	At need	1	At need	?	To be arranged	At need	In accordance with study*

* Oak Ridge Institute of Nuclear Studies. Many different types of special courses can be arranged.

examination. The two groups of courses are summarized in the tables (Table I, II and III).*

Some of these courses are being given this year for the first time, others have been offered for several years. The total number of trainees reported up to July, 1957 is about 1,000; about 300 of these are from short courses and 700 from longer ones. About half the courses are offered once a year, others more often. In some institutions where only 1 or 2 students are taken at a time, groups start frequently. About half the courses are reported as being filled to capacity; some of those which are not are being given this year for the first time and will doubtless have more enrollments later.

Table I presents the short courses, which in general should be considered mainly as introductory and leading to very limited licensure. They are rather widely distributed throughout the country. Directors of two of these encourage their students to keep on coming back afterward for more

* The complete list of clinical isotope courses can be obtained by writing to the author.

TABLE III

LONGER COURSES WITH MORE THAN FIVE STUDENTS

Location	Time Spent	Number Enrolled	No. of Laboratory Periods	Final Examination	Fee	No. of Times Given/Year	Authorization Expected
California	1 eve./wk. for 20 wk.	15	Demonstration only	Yes	Resident $25 Nonresident $50	1	Basic only
California	1 eve./wk. for 20 wk., after course above	5	12		$112	1	Most usual, after this course and preceding one
Texas	1 mo.	12	15(?)	Yes	$100	2	All usual
Pennsylvania	1 da./wk. for 16 wk. (not all M.D.'s)	36	25	Yes	$125	2	All usual
Pennsylvania	1 mo.	36	25	Yes	$125	1	All usual
California	1 eve./wk. for 40 wk. plus 10 full da.	12	17	Yes	$700	1	Any accepted
New York	1 afternoon wk. for 17 wk.	20	10	Yes	$250	1	All usual
New York	1 afternoon/wk. for 8 mo.	24	15	Yes	$300	1	All usual
New York	1 mo.	24	15	Yes	$300	1	All usual
Navy*	26 wk. full time	At need	Many	Yes		1	All usual
Massachusetts	1 mo.	6–8	10–15	?	$300	1	All usual
California	40 sessions during year	Varies	15	?	$575		All usual

* Open only to members of the Armed Forces.

clinical experience on an informal basis. These short courses are likely to be weak on basic physics and basic laboratory training because of the limited time available. They should not be offered for any wide licensure, nor for the American Board of Radiology examination.

The more comprehensive courses fall into two groups, those with very small enrollments and training on the order of a preceptorship, and the larger and more formal ones. The first group are summarized in Table II. There are not many of them and they cannot accommodate very many students in the course of a year. In a busy medical school or hospital department, the opportunity for actual clinical contact in this sort of program should be much greater than in the formal course. The responsibility of the supervisor is greater, in a sense, for he must make sure that the basic theory and laboratory work are properly fitted into this schedule, and this may be neglected when there are no regular classes. The student may miss the stimulus of study with his classmates, but this is compensated for by the much closer association with his clinical chiefs.

The larger courses are listed in Table III. With the exception of the Navy course, which is open only to members of the Armed Forces, only four are full-time, the others meeting once or twice a week for extended periods. Two of the full-time courses are duplicated in extended ones. It is obviously impracticable for a practicing physician to go far from his home for a course meeting once a week for several months. It is also usually difficult for him to take a full-time course which lasts longer than a month. There appears to be a great need for more courses of the full-time, one-month type. In our own case, the full-time course is limited to physicians not living within easy commuting distance of New York City. Its registration is always at capacity several months before the scheduled starting date; I am sure others would be as well attended.

There is a possible argument as to whether the one-month full-time course is as satisfactory as the more diffuse one. We have taught both kinds for three years, and we are not sure. In the one month period, the student has no other interests and continually associates with his classmates, not only in lectures and laboratories but at meals and in study periods. He becomes "saturated" with isotopes. In the longer course, there is more time for assimilating the material, and for following patients. But the student's interests are distracted; he seldom has time to discuss things with his classmates, and may not have much time for study in his already busy life.

With the continual growth of isotope usage, there is an increasing need for teaching in the field. The present courses are doing a great deal, but there is need for more widespread opportunity for postgraduate study in both basic and clinical aspects of the subject.

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STUDY OF THE HEMOSTATIC AND COAGULATION DEFECT IN PATIENTS DURING ROENTGEN THERAPY, WITH PARTICULAR REFERENCE TO LEUKEMIAS AND MALIGNANCIES*

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THE introduction of technical improvements for the study of blood coagulation made possible new investigations of the effect of ionizing radiations on the coagulation and hemostatic mechanisms of the blood. Recent observations have shown that the most prominent change is a platelet defect, revealed by a decreased platelet count and a decreased prothrombin utilization. Hemorrhagic manifestations were chiefly observed in experimental conditions following exposure to atomic radiations.[1,2] In irradiated animals, the presence of a heparin-like anticoagulant was postulated, but this finding was questioned and variously interpreted. Details of the investigations on the effect of ionizing radiations on blood coagulation were reported in our previous paper.[4]

The purpose at this time is to analyze the complex hemostatic and coagulation changes in patients during roentgen therapy by using techniques (a) for the individual estimation of the different coagulation factors, (b) for their evaluation in the mechanism as a whole, and (c) for the study of the elastic properties of the clot, and the relation of these to hemostatic function. Evidence for existence of a combined plasma and platelet defect due to irradiation is presented in this paper. The chronologic sequence of these changes is emphasized, and stress is laid on the value of thrombelastography in such investigations.

MATERIAL AND METHODS

Fifty-one patients were studied in this group and classified according to their disease. All received roentgen therapy. The relevant technical data are indicated below.

The following methods were used in the coagulation studies: (1) *Whole blood clotting time* in siliconed and non-siliconed tubes;[3] (2) *heparin and urea tolerance tests;*[3] (3) *prothrombin time;*[3] (4) *assay of factor* VII *and labile factor;*[3] (5) *platelet count;*[3] (6) *thrombelastography:* the Hellige thrombelastograph was employed as described elsewhere. All determinations were made on recalcified, oxalated plasma, by mixing 0.25 ml. of plasma with 0.1 ml. of 1.29 per cent calcium chloride. The reaction time (*r*), the clot formation time (*k*), and the maximal amplitude (*ma*) were evaluated. The relations between the different values were estimated by plotting *r* against *k* and *r* against *ma*;[5,6] (7) *streptokinase activated fibrinolysis:* a mixture of streptokinase and streptodornase (varidase), briefly indicated as SK, was used in all experiments. Varidase was kindly supplied by Lederle Laboratories Division, through the courtesy of their representative in Italy. Various dilutions of SK were prepared containing 1,000, 750 and 500 units of streptokinase per milliliter respectively. Oxalated plasma (one part of 0.1 M sodium oxalate and nine parts of blood) was mixed with SK (one part of SK and nine parts of oxalated plasma). The final concentration of SK in the plasma was 100, 75 and 50 units per milliliter. Thrombelastographic determinations were performed on the mixture of oxalated plasma and SK by adding 0.1 ml. of 1.29 per cent calcium chloride to 0.25 ml. of the mixture.

* From the Clinica Medica (Director: Prof. P. Introzzi) and the Istituto di Radiologia (Director: Prof. A. Ratti), University of Pavia, Pavia, Italy.

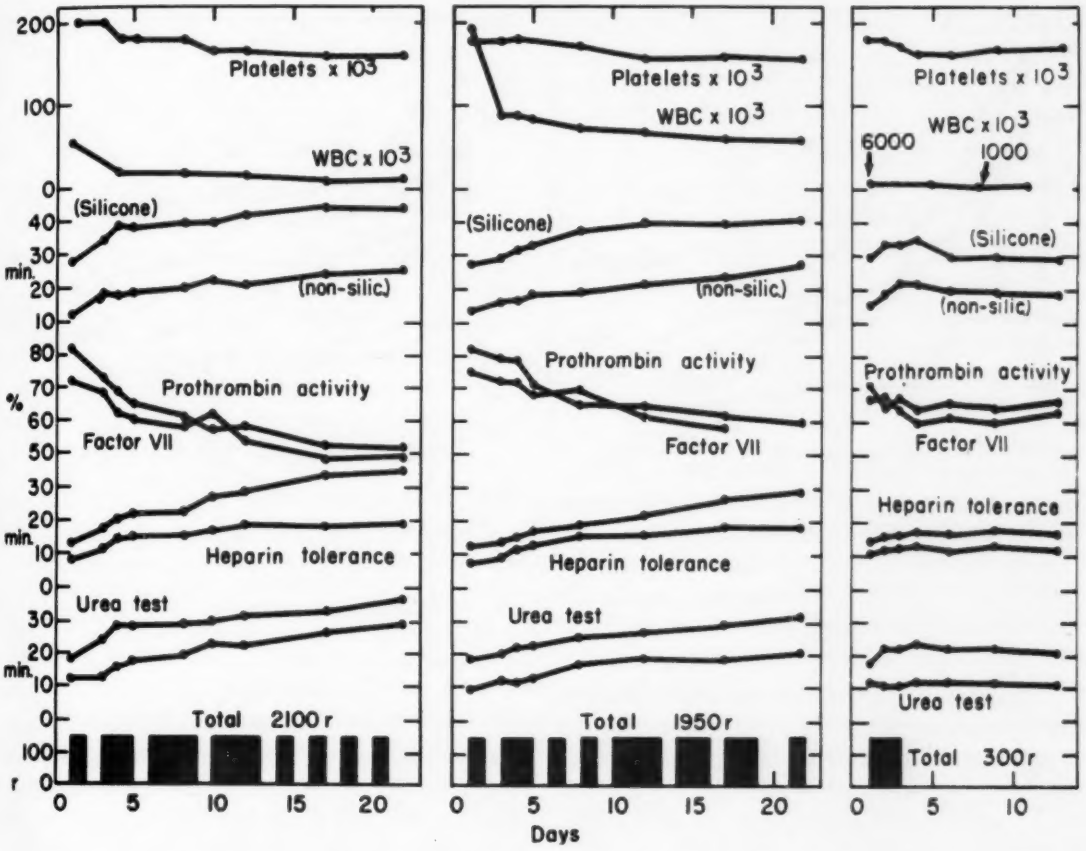

FIG. 1. Examples of coagulation tests in leukemia patients while undergoing roentgen therapy.

The lysis time and the maximal amplitude of the thrombelastogram were evaluated in the experiments.

The technical factors of roentgen therapy were as follows: (1) *Mammary carcinoma.* A total dose of 2,400 to 2,600 r was administered through a single field 24 by 30 cm., with 180 kv., 0.25 mm. Cu plus 1.0 mm. Al filtration, 15 ma. and 60 cm. skin-target distance. The daily dose was 200 r. An additional supraclavicular field was irradiated with 200 kv., 1.0 mm. Cu plus 1.0 mm. Al filtration, 10 ma. and 40 cm. skin-target distance. (2) *Leukemias.* In the myeloid leukemias the spleen was irradiated through three fields (anterior, lateral and posterior). The total dose varied between 1,500 and 2,000 r, with a daily dose of 150 r. The factors used were 200 kv., 0.5 mm. Cu plus 1.0 mm. Al filtration, 10 ma. and 40 cm. skin-target distance. In the lymphatic leukemias the lymph nodes were irradiated with the same technical factors as above. (3) *Malignancies and tumors of the female genitalia.* The daily dose was 200 r, which was administered with 200 kv., 1.0 mm. Cu plus 1.0 mm. Al filtration, 10–20 ma. and 40–50 cm. skin-target distance. The total dose varied between 9,000 and 13,000 r. (4) *Hodgkin's disease.* In all patients, the mediastinal lymph nodes were involved. The mediastinum was irradiated through two fields (anterior and posterior) 10 by 15 cm. in size. The factors were the same as in malignancies and the total dose amounted to 6,000 r. (5) *Arthrosis.* The lumbosacral region was irradiated through a single field 10 by 15 cm. every second day. The daily dose was 100 r up to a total dose of 600 r. The factors were 180 kv., 0.5 mm. Cu plus 1.0 mm. Al filtration, 8 ma. and 40 cm. skin-target distance.

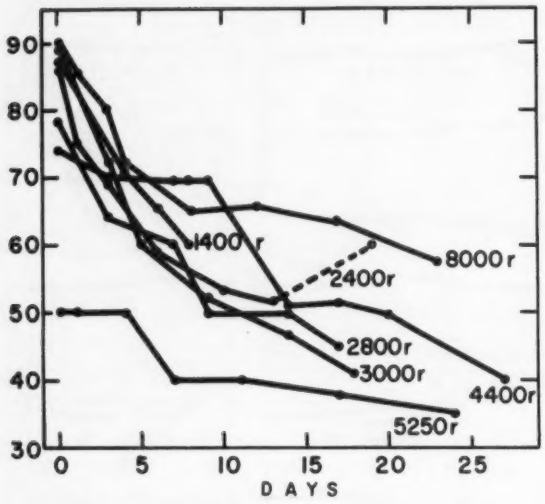

FIG. 2. Behavior of prothrombin activity in a group of malignancies during roentgen therapy. Evident decrease of the values.

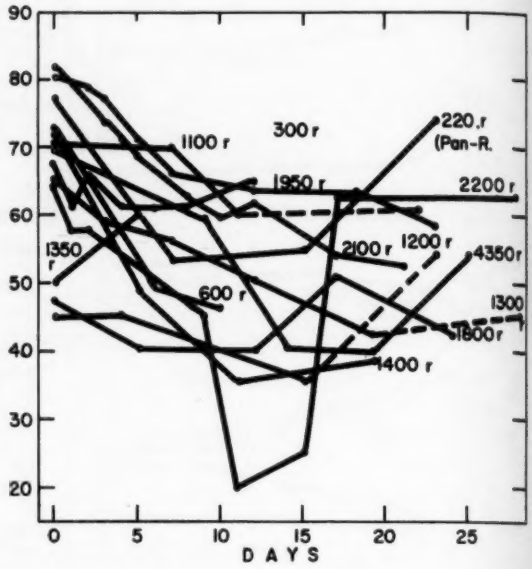

FIG. 3. Behavior of prothrombin activity in a group of leukemia patients during roentgen therapy. The decrease of the values is less constant than in the previous group.

RESULTS

The changes observed during radiation therapy were analyzed separately with respect to the various tests performed. Some typical examples, including the whole series of investigations, are shown in Figures 1, 5, 6 and 7.

(1) *Whole Blood Clotting Time.* In all cases a greater or lesser prolongation of the whole blood clotting time in siliconed and non-siliconed tubes was observed during treatment. There was no correlation between the degree of these changes and the total dose. In the majority of cases prolonged clotting time became evident on or about the tenth day of treatment.

(2) *Heparin and Urea Tolerance Tests.* An increased sensitivity to heparin and urea *in vitro* was found in almost all cases. Such changes were more constant and pronounced than those observed in the whole

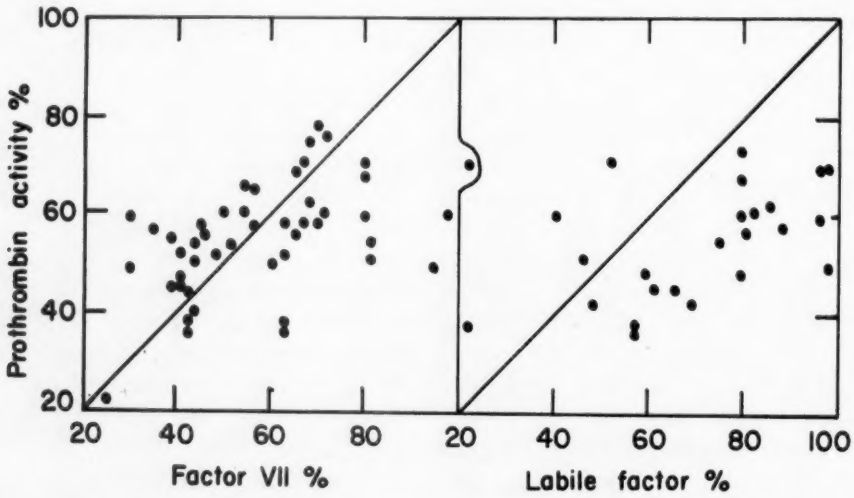

FIG. 4. Correlation of prothrombin activity, factor VII and labile factor.

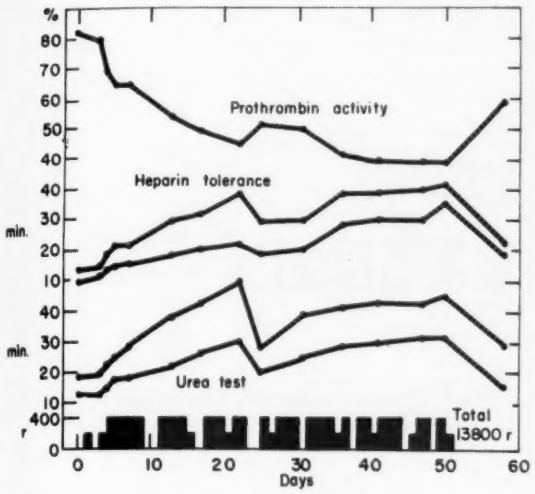

Fig. 5. Changes during roentgen therapy of prothrombin activity, heparin tolerance and urea tests in a case of sarcoma.

blood clotting time, although they followed a similar general pattern.

(3 and 4). *Prothrombin Time, Factor* VII, *Labile Factor.* In general, this group of tests was characterized by a progressive and consistent decrease of the values following radiation treatment. This finding was particularly evident in irradiated malignancies as indicated in Figure 2. In leukemias, the decrease of prothrombin activity, factor VII and labile factor was less constant (Fig. 3). By plotting the values of prothrombin activity against those of factor VII and labile factor, respectively, some correlation was detected between the prothrombin activity and the factor VII, while labile factor values were consistently above prothrombin activity values (Fig. 4).

(5) *Platelet Count.* Irregular changes were observed, mostly in the direction of a decrease of platelet count. No correlation could be established between these findings and the behavior of the other factors, or the total administered dose.

(6) *Thrombelastography.* An increase of the maximal amplitude was frequently observed at the beginning of the treatment, in most cases up to a total dose of 800 r. Afterward, a decrease of the readings occurred. Such a change was not persistent, as the initial values were subsequently reached during the treatment. No definite relationship could be established between such alterations and the following factors: nature of the disease, size of the field, single dose, total dose. The clot formation rate k was modified in the opposite direction to that of the maximal amplitude. The reaction time was not appreciably affected.

By plotting the r values against the k and ma values, respectively, the reciprocal relationship between these values is clearly demonstrated (Fig. 8).

(7) *Streptokinase Activated Fibrinolysis.* At the beginning of the treatment, a reduction of the lysis time was often observed. Subsequently, no constant and significant variations were noticed, unless very high total doses were reached. Under these conditions, definitely prolonged lysis times were evident. The relationship between the lysis time and the corresponding maximal

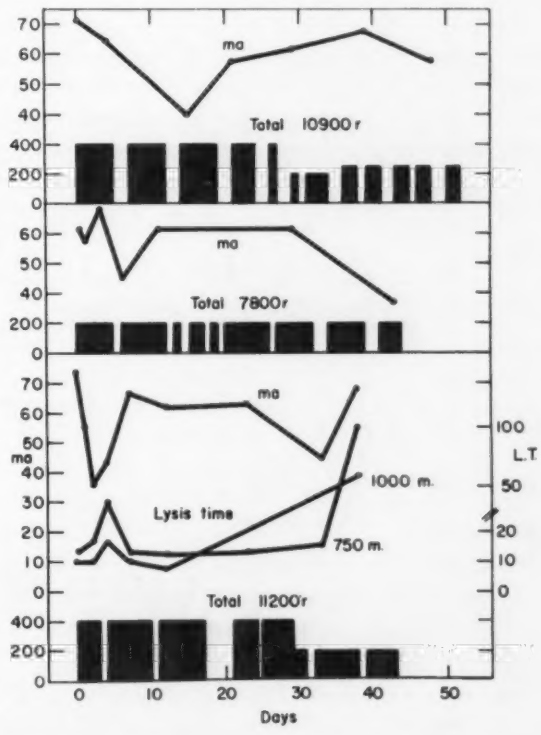

Fig. 6. Thrombelastographic values and lysis times during roentgen therapy in 3 cases of malignancies.

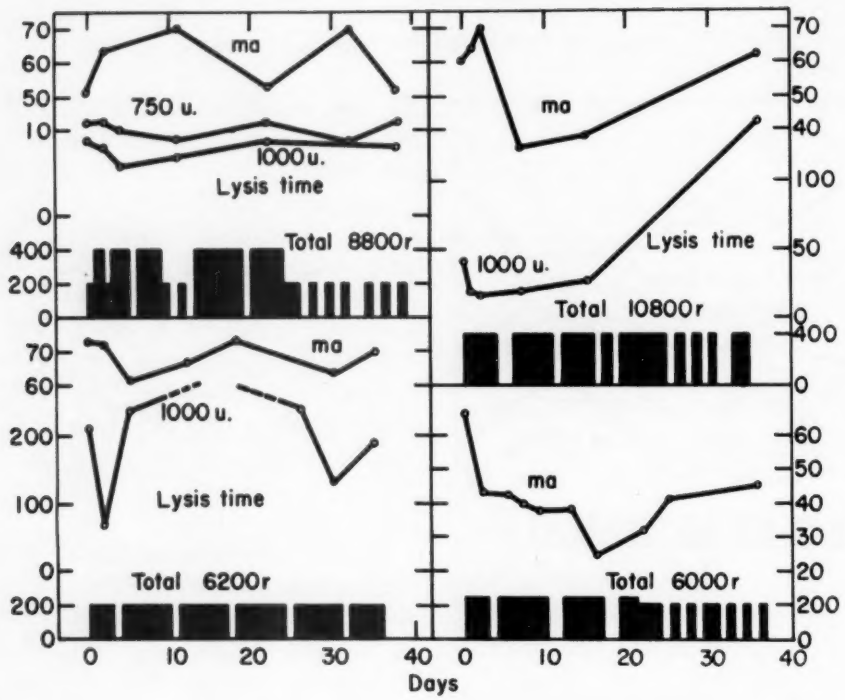

FIG. 7. Further examples of changes in the thrombelastographic values and lysis times after roentgen therapy in cases of malignancies.

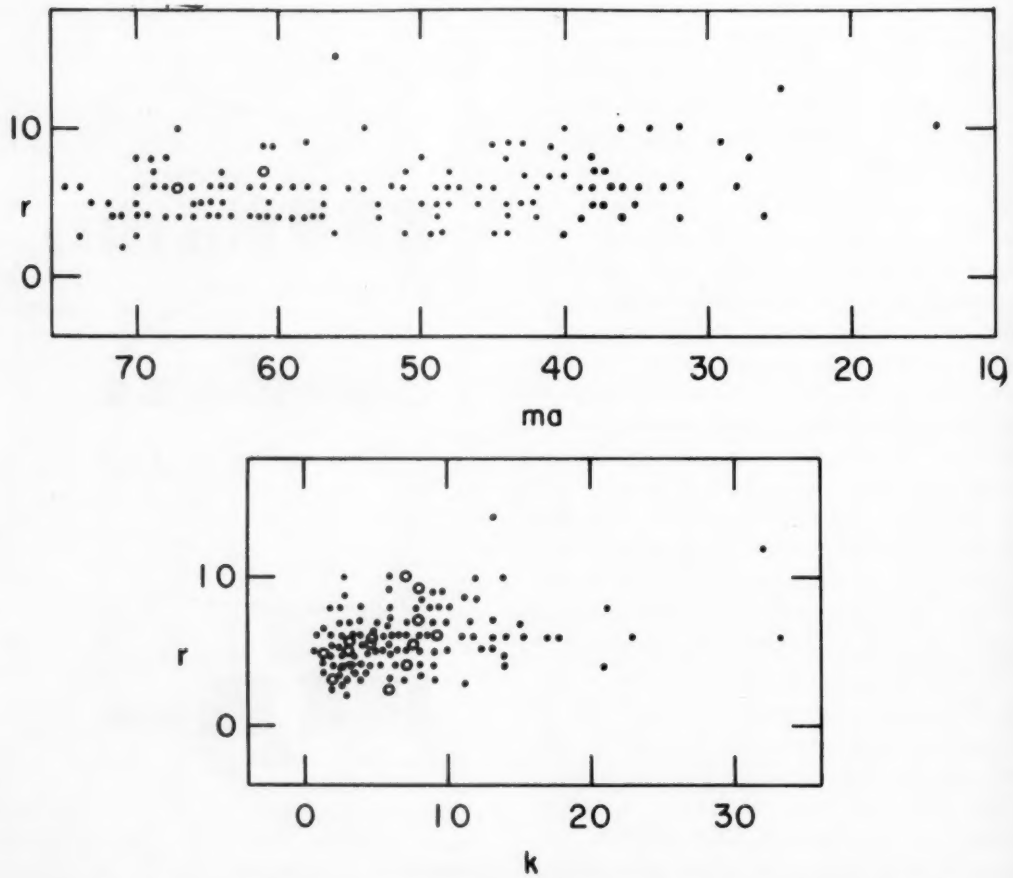

FIG. 8. Correlation of reaction time *r*, clot formation time *k* and maximal amplitude of the thrombelastogram in irradiated patients.

amplitude is shown in Figure 9. For values above 10 mm., the resulting curve approached the straight line.

DISCUSSION

During irradiation with the usual therapeutic doses, as administered in the present study, the changes in the whole blood clotting time were of slight degree and did not usually reach the marked prolongations observed following exposure to massive irradiations. More pertinent information can be obtained by applying other tests. These are not limited to the study of platelet function and number, as already described in other investigations, but also concern the behavior of isolated factors and the modification of the whole coagulation mechanism. The most significant results were obtained by analyzing prothrombin activity, factor VII and labile factor, which often showed a definite diminution. Such findings should be compared with the changes of the heparin and urea tolerance tests. It is assumed that such tests indicate a general alteration of blood clotting and not necessarily the presence of heparin in the blood. There is, however, much evidence that heparin tolerance is markedly influenced by platelets. The results obtained suggest that, under the experimental conditions, heparin tolerance might be influenced also by variations of plasmatic factors, as the similarity of the respective curves seems to show. A concomitant impairment of platelet function is not to be ruled out, even in the presence of slight decreases of platelet counts.

Thrombelastographic examinations give further support to this concept. Typical reductions of the maximal amplitude were observed, as can be seen in thrombocytopenias. Our previous work on thrombelastography has clearly indicated the difference between this pattern and the patterns of other conditions, such as hemophilic and thrombocytopenic blood.[6]

In the study of streptokinase activated fibrinolysis, a prolongation of the lysis times is usually considered to indicate a tendency to hypercoagulability, while a shortening of the lysis time should correspond to hypocoagulability. The behavior of this test follows, as a rule, the patterns of the diphasic reactions, although a great variability is often observed.[7]

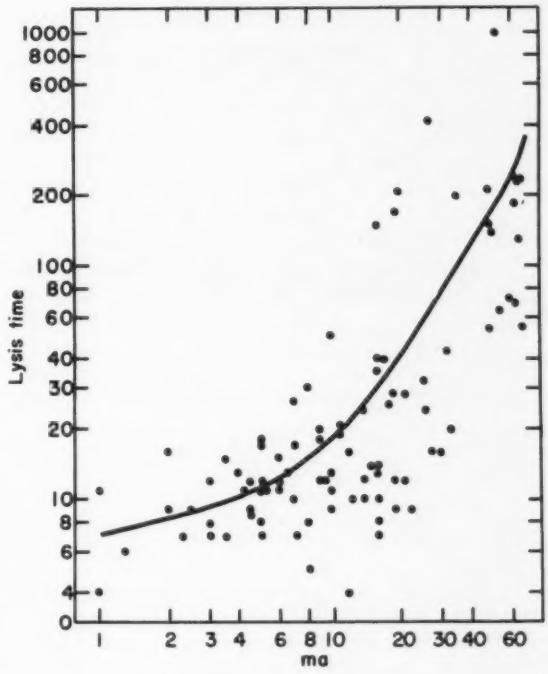

FIG. 9. Correlations of lysis time and maximal amplitude.

SUMMARY

In 51 cases of leukemia, malignancy and other conditions, the behavior of various coagulation factors and mechanisms was studied during roentgen therapy. The most significant changes were as follows: decrease of prothrombin activity, factor VII and labile factor; decrease of heparin and urea tolerance; and reduction of the maximal amplitude in the thrombelastogram. These findings were particularly evident after the administration of at least 800 r. They suggest the presence of a complex coagulation and hemostatic defect, both plasmatic and thrombocytic in nature.

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THE ATMOSPHERIC PRESSURE CORRECTION FACTOR IN ROENTGEN-RAY DOSE MEASUREMENT

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THE measurement of roentgen-ray doses with ionization chambers is subject to the well known temperature and pressure corrections which can amount to several per cent. A rise in temperature, lowering the air density, leads to the correction factor

$$\frac{273+T}{273+22}$$

assuming the instrument has been calibrated at 22° C. (T = temp. in° C). Similarly a variation in atmospheric pressure gives the additional factor 760/P (P = pressure in mm. Hg). Simple correction instruments, which measure directly the combined effect of these two variables, have been described.[2,4,5]

Most of the large cities of the world lie near sea level, and under normal atmospheric conditions the combined correction factor is usually less than 5 per cent. However, it has been pointed out that in radiation therapy hospitals lying at higher altitudes the pressure correction assumes major proportions. For example, Mexico City, the center of the Eighth International Radiological Congress is at a height of 7,474 feet with an average pressure of 586 mm. Hg and requires a pressure correction of about 30 per cent. (The temperature correction works in the same direction if the temperature rises above 22° C.) A list of populous areas where the correction factor is normally greater than 5 per cent is given in Table 1.

Where the mean pressure is not known it has been calculated from the International Civil Aviation Organization Standard Atmosphere Manual for that altitude.[1] These figures will be altered slightly in some instances since the pressure picture over a plateau differs from that over mountains and furthermore is different in tropical regions compared with temperate zones. The table therefore is only a guide and for accurate calibrations the temperature and

TABLE I

CITIES WHERE PRESSURE CORRECTION FACTOR IS SIGNIFICANT FOR ACCURATE ROENTGEN RAY CALIBRATION

	Height (feet)	Average Atmospheric Pressure[3] (mm.Hg)	Pressure Correction Factor
Zurich, Switzerland	1,557	721	1.05
Munich, Germany	1,739	716	1.06
Sofia, Bulgaria	1,804	715	1.06
Innsbruck, Austria	1,968	710	1.07
Alice Springs, Australia	2,000	710	1.07
Madrid, Spain	2,149	707	1.07
Edmonton, Canada	2,146	704*	1.08
Jerusalem, Israel	2,485	694*	1.10
Ankara, Turkey	2,910	682*	1.11
Bangalore, Mysore	3,021	680*	1.12
Calgary, Canada	3,389	670*	1.13
San José, Costa Rica	3,730	661*	1.15
Teheran, Iran	4,002	656*	1.16
Salt Lake City, Utah	4,374	651	1.17
Salisbury, S. Rhodesia	4,880	642	1.18
Pueblo, New Mexico	—	642	1.18
Guatemala, Guatemala	4,856	632*	1.20
Denver, Colorado	5,279	623	1.22
Kabul, Afghanistan	5,895	610*	1.24
Nairobi, Kenya	5,900	609*	1.25
Johannesberg, S. Africa	5,925	608*	1.25
Mexico City, Mexico	7,474	586	1.30
Darjeeling, Bengal	7,376	577*	1.31
Bogotá, Colombia	8,730	558	1.36
La Paz, Bolivia	12,001	494	1.54
Lhasa, Tibet	12,238	480*	1.58

* Pressure calculated from International Civil Aviation Organization Standard Atmosphere Manual.[1]

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pressure should of course be noted at the time and place of measurement.

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Vol. 79, No. 1

THE STANDARDIZATION OF VICTOREEN CONDENSER R-METERS

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THE practical measurement of roentgen-ray dosage in roentgens is usually carried out using substandard dosimeters. Such dosimeters are calibrated against standard ionization chambers which, for roentgen rays generated over the excitation potential range 5 to 500 kv. are of the free air type.

Probably the most commonly employed substandard dosimeter in practical use is the Victoreen condenser r-meter, and this is usually calibrated by placing the thimble condenser chamber in a beam of known quality and dose rate for a known time, noting the registration and deriving a correction multiplication factor. This method has several disadvantages: (1) Even when precautions are taken to stabilize the excitation potential, the tube current, etc., of the roentgen-ray generator, it is difficult to keep the dose rate constant to better than 0.3 per cent over long periods;[6] (2) the readings on the Victoreen electrometer can be distinguished with an accuracy at best of 0.5 per cent; (3) when heavily filtered beams are used, the time taken for individual readings is uncomfortably long; (4) temperature and atmospheric pressure readings and corrections must be made.

A method which eliminates these and other disadvantages has been used by the writers over the last three years. The essential elements of this procedure will be described.

PRINCIPLE OF QUALITY CALIBRATION

The Victoreen dosimeter may be divided into a thimble chamber and an associated electrometer. The response of the chamber to roentgen-ray beams of various qualities is a property of the thimble wall, central electrode material and length, and the volume of air enclosed,[2] while the registration of the electrometer is a property of the electrical characteristics (capacitance and deviation of the fiber as a function of impressed voltage) of the Victoreen system related to its scale. Essentially, the Victoreen is a two-element capacitor with microscopic observation of the position of part of the inner totally enclosed electrode. The quality response may be gauged by the examination of the thimble chamber condenser stem alone, and an absolute calibration done by linking this response with an electrical calibration of the Victoreen system. This enables changes in calibration to be sheeted home to changes in the thimble wall, inner electrode and air volume, to changes in the total capacity of the system or to changes in the position of the fiber as registered by the scale for a given voltage on the fiber.

OUTLINE OF METHOD

Relative Quality Correction Determination. A roentgen-ray beam of known quality passes first through a monitor chamber of mesh type and then through a free air chamber. A charge comparator based upon Townsend's null method of charge measurement indicates the ratio of charges generated in the free air-monitor chamber pair. In this comparator the compensating potential is produced by the monitor ionization charge and a variable range capacitor. For such work a Kemp[3] comparator can be used if an electrometer of adequate sensitivity is available, for it is necessary to guard against the field distortion produced if the collector potential rises appreciably above that of the earthed guard plates.

Replacing the free air chamber by the thimble chamber, roentgen rays are passed

through both monitor and thimble and the comparator indicates the ratio of charge generated in the thimble monitor pair. The ratio of these ratios gives the relative response of the thimble-free air chamber pair. Such a ratio is independent of temperature and pressure changes during the course of measurement as such variations affect the monitor, free air and thimble chambers alike. The ratio is also independent of variations of output of the roentgen-ray generator. Using an induction calibrated comparator[4,5] these final ratios could be determined with an accuracy of approximately 0.03 per cent.

Relation of Charge-ratios to Electrical Calibration of Victoreen. Let the free air chamber have an effective volume of v cm.^{3} (as defined by the product of aperture area and collector width). For reasons of algebraic simplicity, let the working conditions be those to which the quality correction factors of Victoreen condenser r-meters are referred, *i.e.*, 760 mm. pressure and 22°C. temperature. This assumption makes no difference to the final form of the expression derived. If charge $\mathcal{Q}_1$ $\mu\mu$ coulomb is collected over an arbitrary time T seconds from the passage of roentgen rays through the free-air chamber, the associated roentgen value is given by

$$r = \frac{2.99776 \times \mathcal{Q}_1 \times 295 \times k}{1000 \times v \times 273}$$

where k is the correction factor for air absorption of the roentgen-ray beam in passing from the aperture to the middle of the charge collector.

Let a thimble chamber be exposed to the same beam for the same time, then a charge $\mathcal{Q}_2$ $\mu\mu$ coulomb is collected. Making the formal assumption that the condenser chamber had been left sited in the Victoreen electrometer socket during the course of exposure of the thimble to roentgen rays we have

$$\mathcal{Q}_2 = C(V_0 - V_n)$$

where C is the total capacity ($\mu\mu$ farads) between the inner electrode and the outer casing of the Victoreen system and V_n is the potential corresponding to division n of the Victoreen scale appropriate to the thimble chamber used.

A potentiometer calibration of the Victoreen electrometer gives the relation

$$F(n) = (V_0 - V_n)/n.$$

where $F(n)$ is usually regarded as constant and with a satisfactory instrument is constant within 1 or 2 per cent for all values of n. Thus we have

$$\mathcal{Q}_2 = C(V_0 - V_n) = CnF(n)$$

or

$$n = \mathcal{Q}_2/CF(n).$$

The Victoreen quality correction factor M is defined as the ratio of r and n so that

$$M = r/n = \frac{\mathcal{Q}_1}{\mathcal{Q}_2} \times \frac{3.23938kF(n)C}{100\,v} \qquad \text{I.}$$

It is clear from a study of expression I that M is a function both of the quality of the roentgen-ray beam and of scale registration n.

If some arbitrary mid scale registration n' is taken as standard (*e.g.*, 10 of the 25 r scale) then the variables may be separated, *i.e.*,

$$M^1 = \frac{\mathcal{Q}_1}{\mathcal{Q}_2}\frac{3.24}{1000} \times \frac{kF(n')C}{v}$$

and

$$M = M^1\frac{F(n)}{F(n')} = M^1 f(n) \qquad \text{II.}$$

M^1 thus contains the quality correction factor, and $f(n)$ (usually taken to be unity) is the scale correction.

If $3.24F(n')C/1000$ is called v' then from II

$$M^1 = \left(\frac{\mathcal{Q}_1 k}{\mathcal{Q}_2}\right)\frac{v'}{v}.$$

The quantity v' may be regarded as the effective air volume enclosed by the thimble chamber if M^1 is unity and is evaluated

purely by electrical means. For a given condenser chamber, Victoreen electrometer and free air chamber system v'/v is constant and the quality correction factor M^1 is derived simply as a product of charge ratio, $\mathcal{Q}_1/\mathcal{Q}_2$, air absorption correction k, and volume ratio v'/v.

A similar procedure is applicable to Siemens dose-rate meters. In this case $v'=3.24\times10^9 a/R$ where a is the volts/scale roentgen/min. and R the resistance in ohms of the appropriate meter resistor. No doubt the principle could be extended to cover a wide variety of clinical dosimeters.

SPEED OF CALIBRATION

The Victoreen system has a total capacitance of approximately 60pF and a discharge to two-fifths of full-scale deflection implies a voltage change of approximately 100 volts. Hence, to use the Victoreen electrometer a charge of 6×10^{-9} coulomb must be liberated in the thimble chamber with an accuracy of observation of 0.5 per cent at the best. Using a comparator, charges of the order of 2×10^{-11} coulombs may be compared with an accuracy of 0.1 per cent. Thus, use of the comparator implies both a time-saving factor of thirty or thereabouts and greatly enhanced accuracy of determination.

THE DETERMINATION OF C

C is the capacitance between the inner electrode of the condenser chamber sited in the Victoreen electrometer together with the fiber assembly and the outer case of the meter and condenser chamber. As the inner electrode is completely surrounded by the outer, C cannot be determined directly. An adaptor shown in Figure 1*B* to replace the thimble cap was constructed and the following procedure was adopted to determine the desired capacitance. The simple bridge circuit shown in Figure 2 was used to measure the unknown capacitances against a standard three element capacitor C_s of value 10.007pF calibrated and constructed at the National Standards Laboratory, C.S.I.R.O., Chippendale, New South Wales. R_2 is a constantan wire resistance box of nominal value 1,000 ohms and R_1 is a pair of constantan resistance boxes, the first box being variable in steps of 1 ohm to a total of 11,110 ohms and the

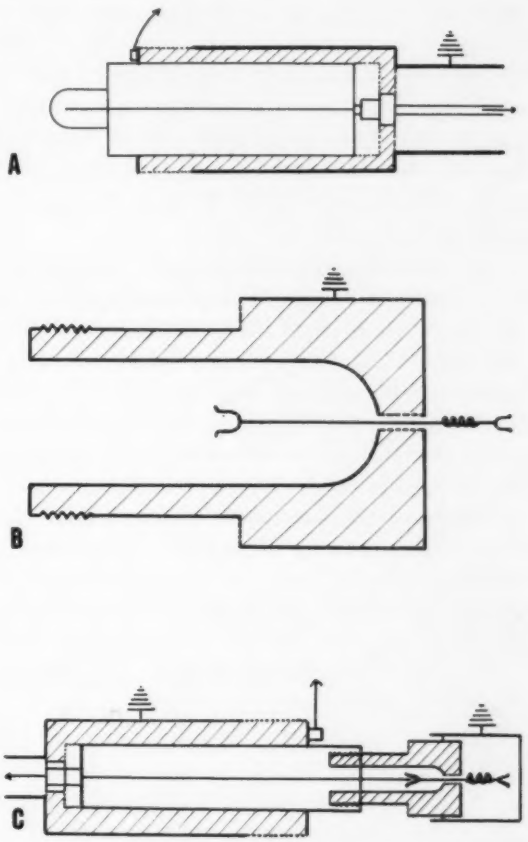

Fig. 1. (*A*) Condenser chamber sited in capacitance measurement socket. (*B*) Thimble chamber adaptor. (*C*) Condenser chamber and adaptor fitted in capacitance measurement socket.

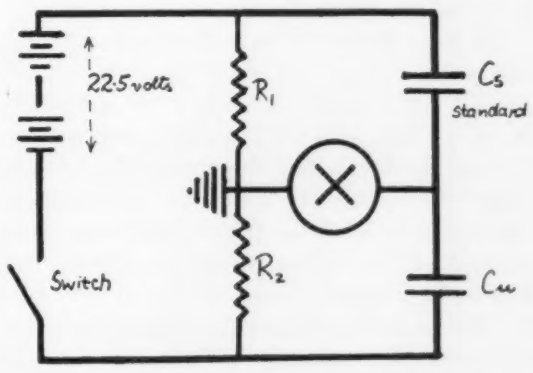

Fig. 2. Capacitance measurement bridge.

second (in series with the first) in steps of 0.1 ohm to a total of 1.1 ohms. The electrometer used was that described by Fry[1] with the addition of a galvanometer register to enhance sensitivity. The working sensitivity was 8,000 divisions per volt. A $22\frac{1}{2}$ volt battery was keyed across the resistances.

The thimble cap was unscrewed from the condenser chamber and the adaptor was screwed in its place. The condenser chamber was then sited in the Victoreen electrometer socket in the usual way. The Victoreen system has now been converted to a three element capacitor and by the use of the bridge circuit of Figure 2 the capacitance between the inner element and the outer case may be measured. This capacitance is called C_3 and may be considered to be composed of the Victoreen capacitance C and a correction term δ due to the substitution of the adaptor for the thimble cap. Thus we have $C_3 = C + \delta$

The correction term δ may be obtained quite simply by siting the condenser chamber (with the adaptor still in position) in the socket illustrated in Figure 1*C*. The condenser chamber has been converted into a three element capacitor and the capacitance C_2 between the inner element and the casing of the condenser chamber can be measured using the bridge. The adaptor is then removed and the thimble cap screwed back into its place (Fig. 1*A*) and the capacitance C_1 measured. The difference between C_2 and C_1 is δ, the change in capacitance due to substitution of the adaptor for the thimble cap.

In practice δ pF may be obtained very simply (if $C_S = 10.007$pF and $R_2 = 1{,}000$ ohms) by noting the difference ΔR ohms between the balance resistance when measuring C_2 and C_1 and dividing by 100. Using high quality resistance boxes, the nominal values of resistance may be taken as being sufficiently accurate to determine a small correction factor

The value of C may be determined certainly to an accuracy of 0.1 per cent by this method. Experience has shown that thimbles may be removed and replaced with an alteration of response to roentgen rays of less than 0.3 per cent. However, as the thimbles are quality calibrated after these procedures have been carried out, such an alteration is only of interest if one wishes to compare old quality correction factors with the new to a high order of precision. Also, at the time of periodic calibration and servicing of the Victoreen r-meter, the thimble caps should be removed to see the state of the graphite inner coating so that such a removal is desirable even apart from its necessity to afford accurate capacitance measurements.

The total capacitance C of the Victoreen system is not sensitive to changes in the siting of the thimble cap, in fact total removal of the 25 r cap reduces the capacitance of the condenser stem by only 0.33 pF. The total capacitance of the Victoreen with a 25 r chamber sited in the electrometer socket has varied between the limits 58.49 and 58.15 pF over eighteen months with the instrument being dismantled twice during that time to service the charger. This gives a range of variation of 0.3 per cent. No detectable change in the total capacitance C was observed when the condenser chamber was rotated in its socket to a variety of positions. The dependence of electrometer capacitance on the position of the observed fiber over the working range was too small to be detected by our methods.

THE DETERMINATION OF $F(n)$

This is conveniently done with a resistance voltage divider and a precision potentiometer as in Figure 3. From this we have $P_n = iR_2$ and $V_n = iR_1$, hence $V_n = P_n R_1 / R_2$.

The Victoreen electrometer was supported on a perspex sheet as it was some fraction of a volt above earth potential. A potential was then impressed on the fiber via a connector sited in the condenser chamber socket, and the fiber oscillated slowly about the scale division three or four times before adjusting accurately so that

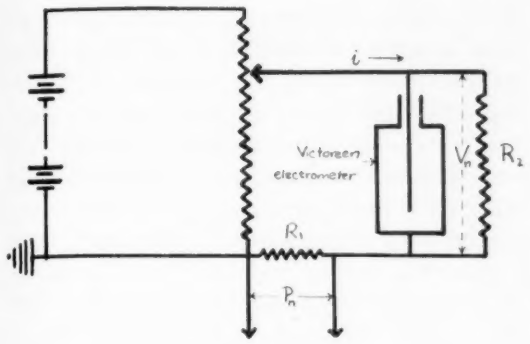

FIG. 3. Voltage calibration circuit.

the fiber passed through the middle of the scale division. Using the precision potentiometer, P_n was measured and V_n evaluated from knowledge of the resistance ratio R_1/R_2. It is desirable to do this at least for $n=0$, 5, 10, 15, 20 and 25 on the 25 r scale. From the expression $F(n)=(V_0-V_n)/n$ one may derive $F(n)$. On a reasonable Victoreen, these values should have a range which is less than 2 per cent. Victoreen No. 3231 was adjusted so that the range of $F(n)$ values was less than 0.3 per cent from $n=5$ to 25 on the 25 r scale. If $F(10)$ is taken as standard, then $f(n)=F(n)/F(10)$ may be taken as a scale correction factor for an instrument which cannot be adjusted to give reasonably constant values of $F(n)$ over the working range. To alter the $F(n)$ characteristics there are three simple adjustments to the meter. The first is the rotation of the fiber mount, the second the alteration of fiber tension and the third the alteration of the position of the field screw sited in the right-hand side of the electrometer case. All that is usually necessary is to alter the tension of the fiber so that the instrument reads 25 r with 150 volts on the fiber and then turn the field screw systematically in or out until sufficient data on $F(n)$ are obtained to determine the optimum position of the screw giving the smallest range of $F(n)$ values. With an electrometer in reasonable condition, adjustment of the field screw is all that is necessary and the best position will be found with a rotation of the screw of less than a quarter of a turn.

Having set the fiber tension and the position of the field screw, examination of the behavior of the Victoreen electrometer reveals that $F(n)$ is dependent on a number of additional factors:

1. The Victoreen may be tilted about either the long or the short axis in the horizontal plane. When the instrument is tilted the earthed fiber position must be adjusted so that it corresponds with the Z mark on the scale. When this adjustment has been made $F(25)$ varies linearly with angular displacement of $\pm$ 6° from the normal position about a horizontal axis parallel to the longest dimension of the electrometer. The change in $F(25)$ for the Victoreen examined was 0.13 per cent per degree of tilt. Tilting the electrometer fore and aft about a horizontal axis indicated that $F(25)$ was quite insensitive to this treatment over 7° of tilt. These measurements indicate that only reasonable care has to be taken in leveling the instrument either for calibration or routine use.

2. One of the recommended preliminary adjustments to the electrometer is that of earthing the fiber and bringing it into coincidence with the Z scale mark. The effect of maladjustment was examined in the following way: As there are no scale divisions in the vicinity of Z, there is no obvious way of identifying the position of the earthed fiber when it is deliberately offset from Z. However, $Z^1=V_0/F(25)$ gives an apparent scale division corresponding to zero potential on the fiber and may be used as a parameter to define the position of the fiber. Examination of a Victoreen indicates the linear dependence of $F(25)$ on Z^1, giving for Victoreen No. 3231 $\Delta F/F=0.56\,\Delta Z^1/Z^1$. Thus with reasonable care in the Z setting, the changes which occur in $F(25)$ are small.

3. When the fiber is charged using the friction wheel, its polarity with respect to the case is negative. In voltage calibrating the instrument, care must be taken to ensure that this condition is observed as the difference in $F(25)$ produced by a

reversal of polarity of the fiber was 0.2 per cent on the instrument examined.

4. An attempt was made to determine the dependence of $F(25)$ on temperature by observing the values of $F(25)$ from day to day. It seems highly probable from these measurements that F(25) increases with temperature rise, the order of the change being 0.5 to 1 per cent for a 10°C. change in temperature. In Adelaide the working temperature range is 12° to 32°, so that at the extreme end of this temperature range it is useful to employ the correction.

5. The focus of the microscope on the fiber is controlled by the setting of a screw on the upper surface of the meter. Rotating this screw through one complete turn indicated that $F(25)$ was dependent on the focus position by approximately 3 per cent per turn or 0.1 per cent for a 10° change. It is clear that the focus screw is not to be tampered with lightly.

6. The viewing tube is screwed into the electrometer case and locked with a hexagonal nut into one of seven or eight possible positions. Investigation discloses that $F(25)$ changes by 0.5 per cent for each complete turn of the viewing tube.

7. Gently bumping the electrometer on its side or base can alter $F(25)$ by as much as 0.4 per cent without visible change in the Z setting. The reason for this is obscure.

Consideration of the above effects indicates that if the electrometer is dismantled and re-assembled it is quite possible to produce changes in $F(25)$ (and hence the quality correction factors) of as much as 5 per cent. Once these sources of change are realized, it is not difficult to re-assemble and adjust so that the change in $F(25)$ is less than 1 per cent. In particular it is emphasized that the focus screw and viewing tube settings must not thoughtlessly be interfered with unless a full voltage calibration is envisaged.

VARIATION IN THE RESPONSE OF THE THIMBLE CHAMBER TO ROENTGEN RAYS

Experience with the calibration of both 100 r bakelite and 250 r nylon chambers indicated that their quality correction factors were a function of orientation in the holding socket for beams softer than 1 mm. Al half-value layer. Orientation about the line of symmetry of the chamber (this axis being normal to the central ray of the roentgen beam) produces changes in quality correction factor of a few per cent for the bakelite chamber and 2 per cent for the nylon chamber for roentgen rays generated at 20 kv. with an inherent filter of 1 mm. Bc and an additional filter of 100 cm. of air. Such variation could be guarded against in practice by marking the condenser chamber and pointing this mark toward the roentgen-ray source during both calibration and normal use.

Examination of the saturation characteristics of the Victoreen thimble chambers indicated that for work of the highest precision dose rate correction factors should be used. Under reasonable working conditions such corrections may be as large as 2 per cent.

ACCURACY OF STANDARDIZATION

On the assumption that a free air chamber which realizes the roentgen precisely is available, the errors which arise in the determination of quality correction factors by this method are as follows: (1) Position errors of order 0.1 per cent in replacing the free air chamber by a thimble chamber; (2) errors of order 0.1 per cent in determining the total capacitance of the Victoreen system; (3) errors of order 0.1 per cent in the determination of $F(n)$. Errors from these sources amount to a possible 0.3 per cent. Over the course of months $F(n)$ is stable certainly to 0.3 per cent when the sources producing change in $F(n)$ given above are avoided. On these considerations quality correction factors should be reliable to 0.5 per cent over considerable periods of time so far as the properties of the electrometer system are concerned.

CONCLUSION

This method of standardizing condenser r-meters has proved to be both rapid and precise. The separation of factors involved in the quality correction multipliers has

enabled sources of change to be located exactly. Sources of error in the standardization of Victoreen r-meters now lie as much with the practical realization of the roentgen using free air chambers as with the Victoreen instrument itself when it is treated with the respect due to a substandard meter. Dismantling of any part of the Victoreen r-meter for service purposes should always be accompanied by a comprehensive re-calibration against primary standards.

SUMMARY

A method is described whereby Victoreen condenser r-meters may be standardized against free air chambers with higher precision. Sources of change in the quality correction multipliers are discussed.

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We are indebted to the late Dr. C. E. Eddy and Mr. J. F. Richardson of the Commonwealth X-ray and Radium Laboratory (Melbourne) for many helpful discussions on the standardization of Victoreen r-meters.

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EFFECT OF ROENTGEN-RAY QUALITY ON RESPONSE IN XERORADIOGRAPHY

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XERORADIOGRAPHY is the method of producing an image of a roentgenographic shadow by the discharge of a uniform electrically charged surface of selenium on a metal plate. The electrostatic image is "developed" by dusting the plate with finely powdered calcium carbonate. The plate is then viewed by very oblique illumination or it can be photographed. Numerous articles have appeared in the literature describing its merits as compared with conventional roentgenography. An interesting phenomenon associated with xeroradiography is the enhancement of local contrast at shadow boundaries due to increase in electrical field strength in this region. Another interesting phenomenon which has not been emphasized is the marked effect of roentgen ray quality on the response of the system. The following experiment brings this out.

A phantom was exposed to 3 qualities of roentgen rays. A single xeroradiographic plate was used. Areas on either side of the phantom shadow were shielded with lead sheets to protect these areas and provide space for the comparison exposures. Exposures were experimentally adjusted to give equal effects on the xeroradiographs for the 3 qualities of radiation. When this was accomplished the values were as shown in Table 1.

It is seen that the process is much less sensitive to the low energy photons. This explains the fact that xeroradiography appears to be much less affected by radiation scatter than does conventional roentgenography, and for the same reason is helped less by the use of a Potter-Bucky diaphragm. It also indicates that with higher kilovoltage and filtration the patient will be greatly protected from radiation damage.

TABLE I

ROENTGEN RAY EXPOSURES TO GIVE ESSENTIALLY EQUAL EFFECTS ON THE XERORADIOGRAPH

Kilovolts Peak	Filter	Approximate Half-value Layer	Mr at Phantom to Give the Same Effect
40	None added	0.5 mm. Al	330
70	1.6 mm. Al.	2.1 mm. Al	84
100	0.25 mm. Cu+ 2 mm. Al	0.23 mm. Cu	57

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Acknowledgment is given to Dr. Ernest McKay, who cooperated in the experimental work and interpretation of the data.

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Vol. 79, No. 1

A PROJECTION ROENTGEN-RAY MICROSCOPE USING ELECTROSTATIC LENSES*

By E. DALE TROUT, B.S., D.Sc., JOHN P. KELLEY, B.S., *and* ARTHUR C. LUCAS, B.S.
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THE possibility of using roentgen rays for the study of minute structure has been under consideration since their discovery. Röntgen is said to have attempted to focus roentgen rays with lenses or reflectors of many materials in an attempt to achieve a point source. In the Sylvanus Thompson Memorial Lecture before the British Institute of Radiology in 1954, Professor J. K. Robertson exhibited the program of the Inaugural Meeting of the Roentgen Society held in November of 1897. Listed on the program is an exhibit of F. H. Neville of Cambridge under the title, "Microskiagrams of Sections of Sodium-Gold Alloys Showing Internal Constitution of Alloys." It is of interest to note that Nixon and Cosslett of this same laboratory have made notable contributions in recent years to a study which must have started almost as soon as Röntgen's discovery became known.[2,3,14]

Since that time many workers have explored various methods that held promise of providing the high resolution or small sources necessary.

Fundamentally, there are three possible ways of achieving the resolution and magnification needed. The simplest and oldest method is contact radiography. This method consists of placing the specimen in contact with a high resolution film or plate and making a radiograph using some available roentgen-ray source, preferably one having a small focal spot and capable of providing soft radiation. The close proximity of specimen to emulsion reduces distortion to a minimum. Magnification is provided by viewing the radiograph under a microscope or by making prints using an enlarger. Much of the literature on microradiography in the fields of biology, medicine, and metallurgy is based on work done using this system. This method has the advantage of simplicity and has provided a considerable body of knowledge. Its chief disadvantage would seem to be the great enlargement that must be provided by the microscope or enlarger. Notable contributions using this method have been made by Sievert,[15] Lamarque, Barclay, Engström[6] and his co-workers, Combée and his associates,[4] and a host of others.

Another method is that which employs a bent crystal or a highly polished metal surface to focus the rays to a point source. The critical angle is small, resulting in the mirror having to be set at a grazing angle to the beam which gives rise to maximum focusing in one plane. This results in an astigmatic image. The system can be improved by using two reflecting surfaces at right angles. Variations of the system have been devised and studied by some very competent and ingenious workers. It could probably provide the ultimate in resolution but would require great skill in its alignment and application. For that reason its usefulness will probably be limited. Major references to this design are found in the works of Kirkpatrick and Baez,[7] Ehrenberg and Spear,[5] and Lucht and Harker.[9]

The third system and one that has received most attention in recent years is projection roentgenography. This, too, is a simple system wherein the specimen is placed as close to the source as possible and the image projected onto the recording medium which is placed at a distance from the source. Magnification is simply the ratio of distances from source to specimen and source to recording medium. In this system the resolution is largely determined by the size of the source and this accounts

* Presented at the Thirty-ninth Annual Meeting of the American Radium Society, Quebec City, Quebec, Canada, May 29–June 1, 1957.

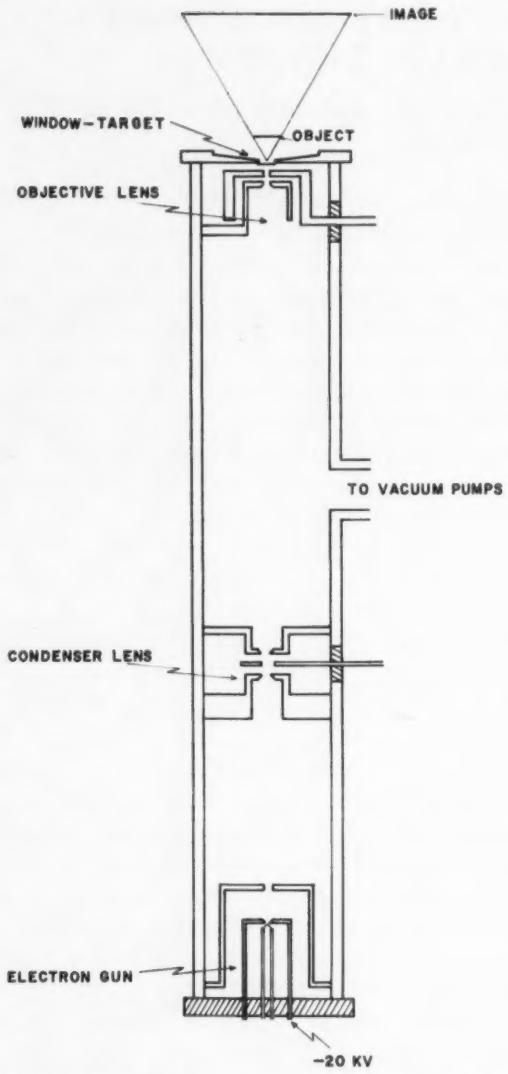

FIG. 1. Diagram showing principal components of the roentgen-ray tube in the roentgen-ray microscope.

for present interest in the method. Increased knowledge in the field of electron optics has made it possible to produce smaller focal spots than were previously possible. Following the pattern of the electron microscope, very fine focus tubes have been built using electromagnetic lenses to focus the electrons on the target. This method has been studied and reported on by von Ardenne[1] and by Cosslett and Nixon.[2,3] More recently, electrostatic lenses have been used in a system that may produce an even more satisfactory design. This system has been described by Newberry and Summers.[12,13]

It is an instrument using electrostatic focusing that is described here. The heart of the system is, of course, the roentgen-ray tube. It consists of an electron gun, an accelerating anode, a condenser lens, objective lens, aperture, and target. The electron beam emerges from the gun and passes through the accelerating anode after which it is collimated by the condenser lens. The collimated beam enters the objective lens where it is demagnified to a focal spot of the order of 1 micron at the target. The target presently in use consists of a 2-mil beryllium window onto which has been plated a very thin layer of tungsten to form the target.

The target thickness is critical since it must stop essentially all the electrons and at the same time be thin enough to permit the transmission of the radiation. The thinnest window possible is also desirable since scattering within the target has the effect of increasing the size of the focal spot. Further complications are injected by the requirement that a target-window must be flat and vacuum tight. Considerable work remains to be done to determine optimum materials and window thickness for various energies.

The tube is entirely demountable since filaments must be replaced after a few hours when used at maximum loading and since tube elements must be cleaned periodically for maximum resolution. The vacuum system consists of a mechanical pump followed by an air-cooled diffusion pump. The mechanical pump is operated continuously. The diffusion pump is operated during periods of use. Working pressure is reached in about five minutes following reassembly of the tube for a change of filament.

The tube can be operated at voltages up to 20 kv. (peak) and tube currents up to 50 microamperes.

Controls and instruments for all elements of the system are located within easy reach of the operator. A specimen manipulator permits control of magnification by

raising or lowering the recording medium through a range of 6 mm., permitting magnifications up to about 100×. Greater magnification can be had by placing the specimen on the tube window rather than in the specimen mount. When the specimen is in the mount, it can be moved in any direction in a horizontal plane through ±4.5 mm.

Apertures of 4, 10, 20, and 40 thousandths of an inch are provided between the condenser and objective lens to reduce spherical aberration. Maximum intensity is provided by the largest aperture but maximum resolution is had with the smallest aperture. The control for aperture selection is located for easy access at the right hand of the operator.

The top plate of the tube which includes the target-window can be replaced by a fluoroscopic screen on a piece of lead glass for observation of the electron beam. The target plate can then be put on and a second check made by putting the fluoroscopic screen on top of the target plate for observation of a test object.

A combination plate and cut film holder is mounted on top of the specimen manipulator. Provision is made for 4 × 5 inch films or plates or for 3¼ × 4 inch lantern slide plates. The plate holder incorporates a fluoroscopic screen for focusing on the plane of the film or plate.

The plate and film holder has provision for attaching a Land-Polaroid camera above it. This makes it possible to get a rapid check on position and focusing. For some rough work the Polaroid print may be adequate in itself. For recording on plate or film, the Polaroid print is useful for once the relative speed of various recording media is known the exposure required for other media can be estimated from the exposure required for the Polaroid print.

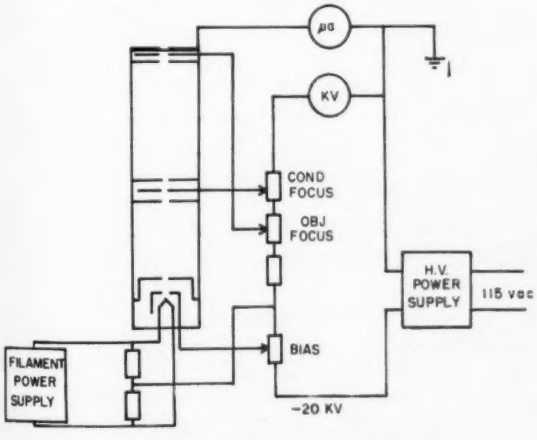

Fig. 2. Simplified schematic diagram of roentgen-ray microscope.

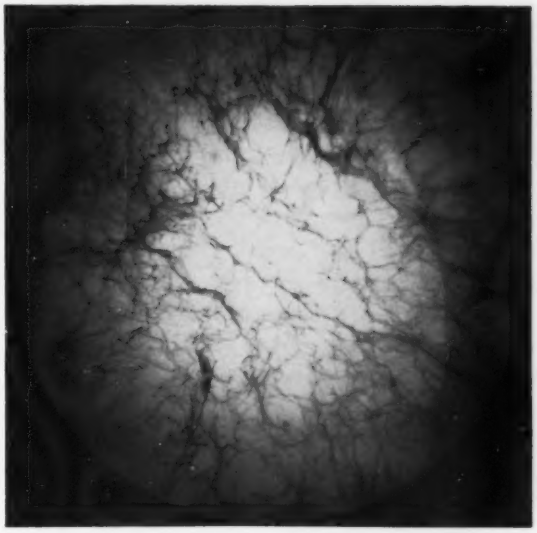

Fig. 3. A section 0.5 mm. thick of freeze-dried human liver. (60×.)

All the controls on the specimen manipulator are calibrated; hence it is possible to make stereoscopic exposures. This is of great value in viewing microradiographs of specimens of considerable thickness where overlying structures may produce confusing shadows.

All the recording devices incorporate an interlock system to protect the operator against operation without protection in the beam.

The field of microscopy is one in which the results obtained are largely determined by the skill and ingenuity of the operator. The preparation of the specimen, the care in lining up and focusing, development, etc., will all have a bearing on the result. An average operator will achieve average results, for no designer or manufacturer can

put into an instrument the skill and care required for optimum utilization of such a device.

One can imagine all kinds of applications for the roentgen-ray microscope in medical and biologic studies. The least that can be said is that it should be possible to visualize minute structures below the surface of the specimen. Careful workers should find resolution of a micron and magnification of a few hundred times quite feasible.

Not the least interesting possibility lies in the study of the effects of radiation on live material which can be observed at intervals without removing it from the field in which it is being irradiated. Some idea of the possibilities may be had from some measurements that we have made which indicate a dose rate of the order of 400 r per minute per microampere at a distance of 1 mm. from the window. Operating at 20 kv. (peak), the half-value layer is 0.35 mm. of unit density material.

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Fortieth Annual Meeting: Hollywood Beach Hotel, Hollywood Beach, Florida, March 27–29, 1958.

EDITORIALS

THE FORTIETH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE Fortieth Annual Meeting of the American Radium Society will take place at the Hollywood Beach Hotel, Hollywood, Florida, March 27, 28 and 29, 1958.

The weather in Florida at this time of year should be ideal for a meeting or a vacation so that a site has been selected which has exceptionally good facilities for both.

The hotel is large and modern. The rooms are air conditioned and there are many of them from which to choose—single, double and suites. The grounds are nicely landscaped with lovely gardens and the hotel is situated directly on the ocean front with one thousand feet of private beach. There is an eighteen hole golf course. There are putting greens and tennis courts and there is an olympic size swimming pool for those who do not like surf bathing.

If you wish to bring your children, the hotel provides planned and supervised recreational activities which will keep them occupied while you are at meetings or otherwise engaged. There are life guards at the pool and on the beach to keep a watchful eye on the venturesome.

The hotel is on the American Plan so that all your meals are included in the daily rate. This also includes your ticket for the Annual Banquet and any other dinner gatherings which do not call for extra services. The cuisine is said to be excellent.

All in all, the Hollywood Beach Hotel would seem to be unsurpassed as a place for the Fortieth Annual Meeting of the American Radium Society.

The time interval between the May, 1957 meeting of the American Radium Society in Quebec City, Canada, and the deadline for publication of the preliminary scientific program for the Florida meeting in March is two months less than the usual time for preparing such a program. Consequently, the program published in this issue of the AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE is not as final or complete as it might have been otherwise.

Requests have been received to present papers on a variety of subjects that should interest the radiotherapist, the surgeon, the medical oncologist and the physicist.

You will note an interesting symposium on chemotherapy and malignancy moderated by Doctor Lloyd F. Craver of New York. You will also note a symposium on carcinoma of the cervix moderated by Doctor A. N. Arneson of St. Louis, Missouri. The names of the essayists on this panel are listed in the scientific program but the titles of their presentations have not as yet been received. It is, however, expected that the material presented will cover radiation therapy including interstitial radioactive gold, and interstitial radium needles as well as other more common radiation procedures. It will also include the classification of cancer of the cervix, time-dose relationship, surgery, and perhaps other interesting data about the disease.

The Janeway Lecture, *Natural Radioactivity in the Human*, will be given by Doctor Leonidas D. Marinelli of Lemont, Illinois, at a dinner Thursday evening and the Janeway Medal will be presented as usual at the Annual Banquet Friday evening.

The ladies have not been forgotten and

plans are underway for a program that should entertain them during the scientific sessions.

It is also planned to end the afternoon sessions at four o'clock which will give some additional free time between the afternoon and evening meetings.

The program as a whole promises to be good, instructive and entertaining as it has been in the past, and we hope that all who can will attend.

Many members of the society and non-members have already made reservations with the hotel, so don't wait too long before developing your own plans and making your own reservations for another get-together.

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85 Jefferson Street
Hartford 14, Connecticut

DOUGLAS J. ROBERTS, M.D.
1892-1957

DOUGLAS JAMES ROBERTS, M.D., of Hartford and Vernon, Connecticut, died suddenly at his home March 12, 1957 of coronary thrombosis associated with lymphatic leukemia.

Doctor Roberts was born in Burlington, Vermont, June 20, 1892. He was educated there and received his college and medical degrees from the University of Vermont. Postgraduate training was obtained at the Royal Victoria Hospital, Montreal, Canada; the Bridgeport General Hospital, Bridgeport, Connecticut; and the Army X-ray School at Cornell University. He

served in the American Expeditionary Force in the first World War as a radiologist and was discharged in 1919 as a major in the Army Medical Corps.

He began the practice of radiology in Hartford, Connecticut, at the termination of his army service, as an associate of Arthur C. Heublein in the private practice of radiology, and also at the Hartford Hospital where he was a visiting radiologist until his death. His skill in his specialty which was immediately recognized and his friendly personality soon led to an outstanding leadership in radiology in and outside the State of Connecticut and in the social affairs of the community.

Doctor Roberts was honored many times by his colleagues. He served as President of the Medical and Surgical Staff of the Hartford Hospital and on many of the hospital staff committees, including the important Chairmanship of the Executive Committee. He was also associated in an active or consulting capacity with several other hospitals in Connecticut. He was a member of many national, sectional and state societies and was past president of the New England Roentgen Ray Society, the New England Cancer Society and the Hartford Medical Society. He had become particularly interested in radiation therapy and at the time of his death was President-Elect of the American Radium Society.

Doctor Roberts had many interests and hobbies outside of his profession. He was a student of nature and loved the outdoors and outdoor activities. He enjoyed competition and his skill was better than average in many sports including skiing, swimming, tennis, hunting and fishing.

He was a student and a collector of antiques and belonged to the Connecticut Historical Society, the Antiquarian and Landmarks Society and the National Association of Clocks and Watches. He was a local authority on many of the things which he collected and nothing gave him greater pleasure than to show his personal collection of antiques which included unusual pieces of pewter, rare old clocks, and period furniture. These were natural settings in the surroundings of an old New England farmhouse which he had restored to its original appearance and beauty.

He loved music and was a patron and a trustee of the Julius Hartt School of Music in Hartford. He himself was endowed with a fine baritone voice and sang with many local groups and with the choir of St. John's Episcopal Church in Rockville, Connecticut, where he was also a vestryman.

Doctor Roberts' genial personality, his generous spirit, and his wide interests made him an enjoyable companion and colleague. He will be missed by his many friends and associates.

Doctor Roberts is survived by his wife, Hope Richardson Roberts; two sons, Doctor Douglas J. Roberts, Jr., who is practicing radiology in Hartford, and Ross R. Roberts; a daughter, Mrs. Jane Roberts Pastel; and a sister, Miss Dorothy Roberts. There are seven grandchildren.

Ralph T. Ogden, M.D.

SOCIETY PROCEEDINGS AND NEWS ITEMS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Shoreham Hotel, Washington, D. C., Sept. 30–Oct. 3, 1958.

AMERICAN RADIUM SOCIETY
Secretary, Dr. Theodore R. Miller, 139 East 36th St., New York 16, N. Y. Annual meeting: Hollywood Beach Hotel, Hollywood Beach, Fla., March 27–29, 1958.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y. Annual meeting: To be announced.

AMERICAN COLLEGE OF RADIOLOGY
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: Feb. 7–8, 1958, Drake Hotel, Chicago, Ill.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. T. Leucutia, Harper Hospital, Detroit 1, Mich. Annual meeting: June 23–27, 1958, San Francisco, Calif.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. Spring 1958 Meeting and Examinations May 19–23, inclusive; Second Special Examination in Nuclear Medicine for Diplomates, May 17, 1958, Palmer House, Chicago, Ill.

NINTH INTERNATIONAL CONGRESS OF RADIOLOGY
Secretary-General, Dr. Hans v. Braunbehrens. Request for information should be addressed to Dr. Viktor Loeck, Kongressbüro, Forsthausstrasse 76, Frankfurt am Main, Germany. Meets in Munich, Germany, July 23 to July 30, 1959.

SIXTH INTER-AMERICAN CONGRESS OF RADIOLOGY
Secretary for North America, Dr. Jorge de la Feor, Hospital Arzobispo Loayzo, Lima, Peru. Meets in Lima, Peru, Nov. 2–8, 1958.

ALABAMA RADIOLOGICAL SOCIETY
Secretary Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

AMERICAN NUCLEAR SOCIETY
Executive-Secretary, Dr. W. W. Grigorieff, P. O. Box 963, Oak Ridge, Tenn. Annual meeting: First week in June, 1958, Los Angeles, Calif.

ARIZONA RADIOLOGICAL SOCIETY
Secretary, Dr. R. Lee Foster, 1313 N. Second St., Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. E. A. Mendelsohn, Holt-Krock Clinic, Fort Smith, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary, Dr. Paul Riemenschneider, Medical College, State University of New York, Syracuse, N Y.

ATLANTA RADIOLOGICAL SOCIETY
Secretary, Dr. Luther Clements, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

BLOCKLY RADIOLOGICAL SOCIETY
Secretary, Dr. Samuel Finkelman, 101 S. Twentieth St., Philadelphia, Pa.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary, Dr. Solomon Schwartz, 555 Prospect Place, Brooklyn, N. Y. Meets first Thursday of each month October through May.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Charles Bernstein, 685 Delaware Ave., Buffalo 9, N. Y. Meets second Monday evening each month, October to May inclusive.

CENTRAL NEW YORK ROENTGEN RAY SOCIETY
Secretary, Dr. Wilbur S. Brooks, 116 E. Castle St., Syracuse 5, N. Y. Meets monthly from October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. Arthur R. Cohen, 41 S. Grant Ave., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL SOCIETY OF NUCLEAR MEDICINE
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. Arthur S. J. Petersen, 11406 Parnell Ave., Chicago 28, Ill. Meets second Thursday of each month, October to April inclusive at the Sheraton Hotel at 8:00 P.M.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. Frederick A. Rose, 2065 Adelbert Rd., Cleveland 6, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

COLORADO RADIOLOGICAL SOCIETY
Secretary, Dr. Lorenz R. Wurtzebach, 601 E. Nineteenth Ave., Denver, Colo. Meets third Friday of each month at Denver Athletic Club.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY
Secretary, Dr. Paul J. Kingston, 114 Woodland St., Hartford, Conn. Meets first Friday in February and April.

DALLAS-FORT WORTH RADIOLOGICAL CLUB
Secretary, Dr. A. H. Keene, 3707 Gaston Ave., Dallas, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. Joseph O. Reed, Jr., Harper Hospital, Detroit, Mich. Meets monthly first Thursday, October through May, at David Whitney House, 4421 Woodward Ave., at 6:30 P.M.

EAST BAY ROENTGEN SOCIETY
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. C. Robert DeArmas 135 Broadway, Daytona Beach, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. B. H. Malone, 1406 Reynolds St., Brunswick, Ga.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary, Dr. George P. Daurelle, Jackson Memorial Hospital, Miami 36, Fla. Meets monthly third Wednesday at 8 P.M. at Mercy Hospital, Miami, Fla.

GREATER ST. LOUIS RADIOLOGICAL SOCIETY
Secretary, Dr. Thomas F. Maher, 634 N. Grand Blvd., St. Louis, Mo.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. John M. Phillips, 1203 Ross Sterling Ave., Houston 25, Texas. Meets fourth Monday each month, Meeting Room, Doctors' Club of Houston.

IDAHO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Alfred M. Stone, St. Lukes Hospital, Boise, Idaho. Meets annually at same time as Idaho State Medical Association.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Illinois Radiological Society
Secretary, Dr. Stephen L. Casper, 1101 Maine St., Quincy, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. C. A. Stayton, 313 Hume-Mansur Bldg., Indianapolis 4, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. James T. McMillan, 1104 Bankers Trust Bldg., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary, Dr. James R. Stark, 3244 E. Douglas, Wichita, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. Robert H. Akers, 1405 West Broadway, Louisville 3, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Ernest I. Melton, 2187 Ocean Ave., Brooklyn 19, N.Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Putnam C. Kennedy, 540 N. Central Ave., Glendale 3, Calif. Meets second Wednesday of month in September, November, March, April and June at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. Francis J. O'Connor, Augusta General Hospital, Augusta, Maine. Meets in June, September, December and March.

Maryland Radiological Society
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

Memphis Roentgen Society
Secretary, Dr. James L. Booth, 899 Madison Ave., Memphis 3, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. H. D. Robertson, Miami Valley Hospital, Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. J. W. Walton, Horton Memorial Hospital, Middletown, N. Y. Meets 8:30 P.M., fourth Tuesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. R. W. Bryne, 3321 N. Maryland Ave., Milwaukee 1, Wis. Meets monthly on fourth Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. O. J. Baggenstoss, 1953 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, once at time of State Med. Assn., and in spring and fall.

Mississippi Radiological Society
Secretary, Dr. Robert P. Henderson, 316 Medical Arts Bldg., Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
Secretary, Dr. John Stewart, 1105 Frederick Lane, Billings, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Jerome Zwanger, 126 Hicksville Rd., Massapequa, L. I., N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. J. F. Kelly, Jr., 816 Medical Arts Bldg., Omaha, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Raymond A. Dillon, 24 Wedgemere Ave., Winchester, Mass. Meets third Friday of each month, October through May, at Hotel Commander, Cambridge, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Harold G. Jacobson, 210th St. and Bainbridge Ave., New York 67, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 4:30 P.M.

North Carolina Radiological Society
Secretary, Dr. William H. Sprunt, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. Marianne Wallis, St. Joseph's Hospital, Minot, N. D. Meetings by announcement.

North Florida Radiological Society
Secretary, Dr. Marvin Harlan Johnston, Five Points Medical Center, Jacksonville 4, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Irving Van Woert, Jr., Albany Hospital, Albany, N. Y. Meets in Albany area on second Wednesdays of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. H. B. Stewart, 2920 Capital Ave., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. Francis C. Curtzwiler, 421 Michigan St., Toledo 2, Ohio. Annual meeting: May 16–18, 1958, Wade Park Manor Hotel, Cleveland, Ohio.

Oklahoma State Radiological Society
Secretary, Dr. Sol Wilner, St. John's Hospital, Tulsa, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. C. V. Allen, Veterans Hospital, Portland, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. Robert W. Hanf, 900 S. Auburn, Kennewick, Wash. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Walter P. Bitner, 234 State St., Harrisburg, Pa. Annual meeting: Penn Sheraton Hotel, Pittsburg, Pa., May 15–17, 1958.

Philadelphia Roentgen Ray Society
Secretary, Dr. Roderick L. Tondreau, 3400 Spruce St., Philadelphia 4, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Edward M. Schultz, 3401 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Hotel Roosevelt.

Radiological Section, Baltimore Medical Society
Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Section, Southern Medical Association
Secretary, Dr. Ted F. Leigh, Emory University, Georgia. Annual meeting: To be announced.

Radiological Society of Greater Cincinnati
Secretary, Dr. Warner Peck, Carew Tower St., Cincinnati 2, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. Jun-chu'an Wang, The Queen's Hospital, Honolulu 9, Hawaii. Meets third Monday of each month alternately at 4:30 P.M. and 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. E. H. Stratemeier, Jr., 1010 Rialto Building, Kansas City 6, Mo. Meets last Friday of each month.

RADIOLOGICAL SOCIETY OF KANSAS CITY
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA
Secretary, Dr. Seymour Ochsner, Ochsner Clinic, New Orleans 15, La. Meets annually during Louisiana State Medical Society Meeting.

RADIOLOGICAL SOCIETY OF NEW JERSEY
Secretary, Dr. Andrew P. Dedick, Jr., 67 E. Front St., Red Bank, N. J. Meets at Atlantic City at time of State Medical Society and in November in Newark, N. J.

RADIOLOGICAL SOCIETY OF NEW YORK STATE
Secretary-Treasurer, Dr. Mario C. Gian, 610 Niagara St., Buffalo 1, N. Y. Meets with the State Medical Society in New York, May 11–16, 1958.

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA
Secretary, Dr. Harold P. Tompkins, 658 S. Westlake, Los Angeles 57, Calif.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.
Secretary, Dr. John W. Colgan, 277 Alexander St., Rochester 18, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: Shirley Savoy Hotel, Denver, Colo., Aug. 14–16, 1958.

ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. Edwin C. Ernst, Jr., 3720 Washington Ave., St. Louis 8, Mo. Meets fourth Wednesday each month, except June, July, Aug. and Sept.

SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets Brooke Army Medical Center Officers Mess second Wednesday of each month.

SAN DIEGO RADIOLOGICAL SOCIETY
Secretary, Dr. J. C. Asher, 2001 Fourth Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

SAN FRANCISCO RADIOLOGICAL SOCIETY
Secretary, Dr. Irma Smith, 450 Sutter St., San Francisco 8, Calif. Meets quarterly at Grison's Steak House.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION
Secretary, Dr. Nathan M. Spishakoff, 405 N. Bedford Dr., Beverly Hills, Calif.

SECTION ON RADIOLOGY, CONNECTICUT STATE MEDICAL SOCIETY
Secretary, Dr. Ralph J. Littwin, Bristol Hospital, Bristol, Conn. Meetings are held bi-monthly.

SECTION ON RADIOLOGY, MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA
Secretary, Dr. Charles E. Bickham, Jr., 1835 Eye St., N.W., Washington 6, D. C. Meets Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY
Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M. September to May inclusive.

SOCIETY OF NUCLEAR MEDICINE
Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. Annual meeting: June 19–21, 1958, Beverly Hilton Hotel, Los Angeles, Calif.

SOUTH BAY RADIOLOGICAL SOCIETY
Secretary, Dr. Howard L. Jones, Palo Alto Hospital, Palo Alto, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. Wayne Reeser, 804 Burroughs St., Conway, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

SOUTHERN RADIOLOGICAL CONFERENCE
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, Mobile, Ala.

SOUTHWESTERN RADIOLOGICAL SOCIETY
Secretary, Dr. Gordon Black, Suite 2-A, El Paso Medical Center, 1501 Arizona, El Paso, Texas. Meets second Tuesday of each month.

TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. G. K. Henshall, 311 Medical Arts Bldg., Chattanooga 3, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

TEXAS RADIOLOGICAL SOCIETY
Secretary, Dr. J. E. Miller, Baylor Hospital, Dallas, Texas. Next meeting, January 24 and 25, 1958, San Antonio, Texas.

TRI-STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Robert E. Beck, 600 Mary St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May, Service Memorial Institute.

UPPER PENINSULA RADIOLOGICAL SOCIETY
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

WASHINGTON STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Eva L. Gilbertson, 1317 Marion St., Seattle 4, Wash. Meets fourth Monday of each month from September through May at 610 Pine St., Seattle.

WEST VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. W. Paul Elkin, 515 Medical Arts Bldg., Charleston, W. Va. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee.

WESTCHESTER RADIOLOGICAL SOCIETY
Secretary, Dr. Arnold Myron Wald, 406 Boston Post Road, Port Chester, N. Y. Meets on third Tuesday of January and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY
Secretary, Dr. Farrell F. Golden, 5221 Tonyawatha Trail, Madison 4, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-RAY STUDY CLUB OF SAN FRANCISCO
Secretary, Dr. John H. Heald, 450 Sutter St., San Francisco 8, Calif. Meets monthly, third Thursday at 7:30 P.M., Children's Hospital, September through June.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPÍA CUBANA
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29y F-Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

SOCIEDAD COSTARRICENSE DE RADIOLOGIA
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

SOCIEDAD MEXICANA DE RADIOLOGÍA, A. C.
Calle del Oro No. 15, México 7, D. F.
Secretary-General, Dr. Guillermo Santín. Meets first Monday of each month.

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 86, Panama, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Empire

Association of Radiologists of the Province of Quebec
Secretary, Dr. Isadore Sedlezky, 3755 Cote St. Catherine Rd., Montreal, Que. Meets four times a year.

British Institute of Radiology Incorporated with the Röntgen Society
Honorary Secretary, Dr. John Blewett, 32 Welbeck St., London, W. 1. Meets monthly from October until May.

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 45, Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1.

Canadian Association of Radiologists
Honorary Secretary, Dr. Guillaume Gill, *Associate Honorary Secretary*, Dr. Robert H. Fraser, 1555 Summerhill, Montreal 25, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
General Secretary, Dr. Louis Ivan Vallée, 1058 rue St-Denis, Montreal 18, Canada. Meets third Saturday each month.

College of Radiologists of Australasia
Honorary Secretary, Dr. Arthur B. Sullivan, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W.

South America

Asociacion Argentina de Radiologia
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151 Córdoba, Argentina. Meetings held monthly.

Sociedad Argentina de Radiologia, Junta Central, Buenos Aires
Secretary, Dr. Juan L. Ambrogna, Montevideo 745, Buenos Aires. Meetings are held monthly.

Sociedad Argentina de Radiologia, Filial del Litoral, Sede, Rosario
President, Dr. Francisco P. Cifarelli. Meets monthly second Wednesday, 19 ha 663 Italia St., Rosario, Santa Fe.

Sociedad Argentina de Radiologia, Filial del Sur, Sede, La Plata
President, Prof. Dr. Jose P. Uslenghi, La Plata. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Centro Sede, Córdoba
President, Prof. Dr. David L. Caro, Corro 86, Córdoba. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Norte, Sede, Tucuman
President, Dr. Julio Mendez Valladares, Rivadavia 358, Tucuman. Meets monthly.

Sociedad Argentina de Radiologia, Filial de Cuyo Sede, Mendoza
President, Dr. J. A. Orfila, Hospital Central, Mendoza. Meets monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiologia
Secretary, Dr. Armando Doberti, Merced 565, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Mejia Dzg., Carrera 13, No. 25-31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuadoriana de Radiologia y Fisioterapia
Secretary, Dr. Enrique Ortega Guzmán, Casilla 4719, Guayaquil, Ecuador.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos G. Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Roberto François, Av. Agraciada 1464, Piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad Venezolana de Radiología
Secretary, Dr. Otto Paz, Centro Médico, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal Caracas.

Continental Europe

Austrian Roentgen Society
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Société Française d'Electro-Radiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, de Centre et du Lyonnais du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord.
Secretary-General, Dr. Ch. Proux, 9, rue Daru, Paris 8e, France. Meets annually.

Ceskoslovensk společnost pro Röntgenologii a Radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Dr. med. Peter Kröker, Evangelisches Krankenhaus, Huyssens Stiftung, (22a) Essen. Meets annually.

Società Italiana de Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Electrologie en Röntgenologie
Secretary, Dr. J. R. von Ronnan, Violenweg 14, den Haag, Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiologia y Electrologia
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgengesellschaft (Société Suisse de Radiologie)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The next list of Meetings of Radiological Societies will be published in the May issue of the Journal.

THE AMERICAN RADIUM SOCIETY

PRELIMINARY PROGRAM

The following is the preliminary program which is being arranged by the Program Committee and the Committee on Arrangements under the Chairmanships of President Ralph T. Ogden and Doctor Robert L. Brown, respectively, for the Fortieth Annual Meeting of the American Radium Society to be held at the Hollywood Beach Hotel, Hollywood-by-the-Sea in Florida, Wednesday through Saturday, March 26, 27, 28 and 29, 1958.

Wednesday, March 26, 1958

Executive Committee

9:30 A.M.–4:00 P.M.

Registration

2:30–6:30 P.M.

Thursday, March 27, 1958

Registration

8:30 A.M.–5:00 P.M.

Opening Session

9:00 A.M.–12:00 M.

Opening of the Fortieth Annual Meeting. Ralph T. Ogden, M.D., Hartford, Conn.

First Scientific Session. Chairman, Milford D. Schulz, M.D., Boston, Mass.

President's Address. Ralph T. Ogden, M.D., Hartford, Conn.

Comparison of Medium Voltage and Supervoltage Roentgen Therapy in the Treatment of Oropharynx Cancers. Gilbert H. Fletcher, M.D., William S. MacComb, M.D., Paul M. Chau, M.D., and Wesley G. Farnsley, M.D., Houston, Texas.

Carcinoma at Base of Tongue. Victor Marcial, M.D., San Juan, Puerto Rico.

Carcinoma of the Nasopharynx. Manuel Lederman, M.D., London, England.

Treatment of Advanced Squamous Cell Carcinoma of the Head and Neck by Interstitial Radium Implantations. Fernando G. Bloedorn, M.D., Baltimore, Md.

Teflon Tube Method of Radium Implantation. Oscar L. Morphis, M.D., Fort Worth, Texas.

Treatment of Cancer of the Esophagus by Rotation Therapy. Enrique P. Viacava, M.D., Buenos Aires, Argentina.

11:45 A.M.

Executive Session
Election of New Members

12 M.–2:00 P.M.

Recess

Thursday, March 27, 1958

Second Scientific Session

2:00–4:00 P.M.

Chairman, Elizabeth F. Focht, New York, N. Y.

Round Table Conference on Chemotherapy in the Treatment of Carcinoma

Moderator, Lloyd F. Craver, M.D., New York, N. Y.

Leukemia, Especially Acute Leukemia. Joseph H. Burchenal, M.D., Attending Physician, Chemotherapy Service of the Department of Medicine, Memorial Center, New York, N. Y.

Chemotherapy of Malignant Lymphomas. Henry D. Diamond, M.D., Associate Attending Physician, Medical Neoplasia Service, Department of Medicine, Memorial Hospital, New York, N. Y.

Chemotherapy of Solid Tumors. Louis K. Alpert, M.D., Clinical Professor of Medicine and Director of the Cancer Chemotherapy Research Program, The George Washington School of Medicine, Washington, D. C.

Studies of Quinoline and Acridine Derivatives of Nitrogen Mustard for the Chemotherapy of Multiple Myeloma and Malignant Lymphomas. Ralph Jones, Jr., M.D., Chairman of the Department of Medicine, University of Miami, Miami, Fla.

The Prophylactic Use of Alkylating Agents in Surgery for Cancer. Robert R. Smith, M.D., Chief, Surgery Branch, National Cancer Institute, Bethesda, Md.

Chemotherapy from the Pathologist's Point of View. Arthur C. Allen, M.D., Professor of Pathology, University of Miami, Miami, Fla.

4:00 P.M.

Adjournment

Thursday Evening, March 27, 1958

6:30 P.M.

Reception
for
Members and Guests
of the
American Radium Society
by the
Radium Chemical Company

7:30 P.M.

Informal Dinner

The Janeway Lecture: Natural Radioactivity in the Human
Leonidas D. Marinelli, M.D., Lemont, Ill.

Friday, March 28, 1958

Third Scientific Session

9:00 A.M.–12:00 M.

Chairman, Theodore R. Miller, M.D., New York, N. Y.

The Metabolic Behavior and Clinical Response of Radioactive Iodinated Rose Bengal in Patients with Inoperable Cancer of the Biliary System. George T. Pack, M.D., and Irving M. Ariel, M.D., New York, N. Y.

The Liver, Radiation and Leukemia. Marion F. Beard, M.D., Louisville, Ky.

Lymphosarcoma of the Stomach. Gordon P. McNeer, M.D., New York, N. Y.

Transverse Tomography—the Third Dimension in Body-section Roentgenography: Applications in Radiation Therapy. Bernard Roswit, M.D., Sol M. Unger, M.D., Joseph Stein, M.D., Stanley J. Malsky, M.A., M.Sc., and Cyprian Reid, B.Sc., Bronx, N.Y.

High-pressure Oxygen and Radiotherapy. Cyril Sanger, M.D., Hartford, Conn.

Pharmacological and Other Means of Modifying the Radiation Response. J. Robert Andrews, M.D., Bethesda, Md.

12:00 M.

Recess

Friday, March 28, 1958

Fourth Scientific Session

2:00–4:00 P.M.

Chairman, Ralph M. Caulk, M.D., Washington, D. C.

Round Table Conference on Carcinoma of the Cervix

Moderator, A. N. Arneson, M.D., St. Louis, Mo.

Willard M. Allen, M.D., St. Louis, Mo.; Manuel Garcia, M.D., New Orleans, La.; James Findlay Nolan, M.D., Los Angeles, Calif.; Gray H. Twombly, M.D., New York, N. Y.; George Willis Waterman, M.D. Providence, R. I.

4:00 P.M.

Adjournment

Friday Evening, March 28, 1958

6:30 P.M.

Reception
for
Members and Guests
of the
American Radium Society

7:30 P.M.

Annual Banquet
Presentation of the Janeway Medal
to
Doctor Leonidas D. Marinelli
Entertainment
Dancing

Saturday Morning, March 29, 1958

Fifth Scientific Session

9:00 A.M.–12:00 M.

Chairman, Jesshill Love, M.D., Louisville, Ky.

Physical and Clinical Advantages and Limitations of Cobalt 60 Teletherapy. 1. Physical Factors. Carl B. Braestrup, Ph.D., New York, N. Y. 2. Clinical Considerations. Ruth J. Guttmann, M.D., Forest Hills, N. Y.

A Precision Cobalt 60 Unit for Fixed Field and Rotation Therapy. Harold E. Johns, Ph.D., Toronto, Ontario, Canada.

Cobalt and Cancer—the Delusion of Depth Dose. Norman Simon, M.D., New York, N. Y.

Progress Being Made in Developing Radioactive Chromium 51 Cylinders for Interstitial Gamma X-Ray Therapy. William G. Myers, Ph.D., M.D., Columbus, Ohio.

Small Sources of Cesium Therapy. W. E. C. Allt, M.D., Toronto, Ontario, Canada.

The Treatment of Pterygium by Surgery and Beta Radiation—an Analysis of 256 Cases. Sidney Rubenfeld, M.D., New York, N. Y.

Executive Session

AMERICAN BOARD OF RADIOLOGY ANNOUNCES EXAMINATIONS

A special examination in Nuclear Medicine for Diplomates in Radiology or Therapeutic Radiology will be held at the Palmer House, Chicago, Illinois, Saturday, May 17, 1958. The deadline for filing applications is February 1, 1958.

The regular examination in Radiology will be held at the Palmer House, Chicago, Illinois, May 19–23, 1958. Candidates finishing their training by June 30, 1958 will be eligible. The deadline for filing applications was January 1, 1958.

The Fall 1958 examination will be held at the Shoreham Hotel, Washington, D. C., December 8–12. Candidates finishing their training by December 31, 1958 will be eligible. The deadline for filing applications is July 1, 1958.

H. DABNEY KERR, M.D.
Kahler Hotel Building
Rochester, Minnesota

LOS ANGELES RADIOLOGICAL SOCIETY TO SPONSOR MID-WINTER CONFERENCE

The Tenth Annual Mid-Winter Radiological Conference, sponsored by the Los Angeles Radiological Society, will be held at the Biltmore Hotel, Los Angeles, California, on Saturday and Sunday, February 22 and 23, 1958.

An outstanding program of pertinent interest has been arranged and the guest speakers will be: Dr. Ralston Paterson, Manchester, England; Professor Wm. V. Mayneord, London, England; Dr. D. L. McRae, Montreal, Canada; Dr. E. B. D. Neuhauser, Boston, Massachusetts; Dr. Robert Stone, San Francisco, California; Dr. L. H. Garland, San Francisco, California; and Dr. G. W. Beadle, Pasadena, California.

The conference fee of $20.00 includes two luncheon meetings featuring questions and answers. A banquet ($7.50 per plate) preceded by cocktails will be held Saturday evening. Reservations may be made through Dr. John H. Eaton, 65 North Madison Avenue, Pasadena, California.

Courtesy cards will be available to residents in radiology and radiologists in the Armed Forces by advance registration, with reduced tariff for the luncheons and banquet. Hotel reservations should be made promptly through the Convention Manager, Biltmore Hotel, Los Angeles, California.

UNIVERSITY OF KANSAS SCHEDULES POSTGRADUATE RADIOLOGY MEETING

The annual postgraduate radiology meeting of the University of Kansas will be held from February 10 to 13, 1958. This meeting is sponsored by the Radiologists of Greater Kansas City, the University of Kansas School of Medicine and the Radiologists of Kansas. An outstanding group of speakers will participate in the program. Further information may be obtained by writing to Dr. G. M. Tice, Department of Radiology, University of Kansas Medical Center, Kansas City 12, Kansas.

CHAMBERLAIN LECTURE PRESENTED BY DR. RUDHE

The second W. Edward Chamberlain Lecture was given at the Temple University Medical School by Dr. Ulf Rudhe, Acting Chief of the Roentgen Diagnostic Department, Caroline Hospital, Stockholm, Sweden, on October 22, 1957. Doctor Rudhe's subject was "Roentgenologic Studies of Functional Anatomy of Outflow Tracts and Valves in Heart Disease."

SEVENTH INTERNATIONAL CANCER CONGRESS TO MEET IN LONDON

The Seventh International Cancer Congress will take place at the Royal Festival Hall, London, England, from July 6 to 12, 1958. Registration forms may be obtained from the Secretary-General, 45 Lincoln's Inn Fields, London, W. C. 2, England.

RADIOLOGIC PHYSICS COURSE TO GIVE DEGREE CREDIT

The College of Physicians and Surgeons of Columbia University has announced a full-time integrated course in radiologic physics leading to the degree of Master of Science, to be given during the academic year 1958–59. Drs. Rossi, Quimby, Rugh, Braestrup, Feitelberg and Gross will cover different phases of radiologic physics and radiobiology, while Drs. Seaman and Kligerman will present clinical applications. Practical laboratory work will be stressed.

Prerequisite for admission is a bachelor's degree, with a major or very strong minor in physics, or equivalent scholastic background, with a good academic record. Tuition for the complete course is $900. The registration will be limited to six. Inquiries should be directed to Dr. Harald H. Rossi, 630 West 168th Street, New York 32, New York.

RADIOACTIVE ISOTOPE COURSE OFFERED

A full-time course in the clinical use of radioactive isotopes will be given under the supervision of Dr. Sergei Feitelberg and Dr. Edith Quimby of the Department of Radiology, Columbia University, New York, New York, from June 2 through June 28, 1958. In addition, the teaching staff includes sixteen invited lecturers from the New York area, each presenting material in his own special field.

Enrollment in the class is limited to 20. The fee is $300. Inquiries should be directed to Dr. Sergei Feitelberg, Mt. Sinai Hospital, Fifth Avenue and 100th Street, New York, New York.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

SOME EFFECTS OF IONIZING RADIATION ON HUMAN BEINGS. Edited by E. P. Cronkite, V. P. Bond, and C. L. Dunham. From the Naval Medical Research Institute, Bethesda, Maryland; U. S. Naval Radiological Defense Laboratory, San Francisco, California; and Medical Department, Brookhaven National Laboratory, Upton, New York. Paper. Pp. 106, with illustrations and tables. United States Atomic Energy Commission, Oak Ridge, Tennessee. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1956.

This book is a report of the on-site study of human beings exposed to the fallout material from an experimental thermonuclear device exploded at Eniwetok on March 1, 1954. The study team was organized from personnel of two Navy laboratories and the AEC Division of Biology and Medicine and the Armed Forces Special Weapons project.

In separate chapters are discussed the radiation characteristics of the fallout material and determination of the dose of radiation, clinical observations and general management, skin lesions and epilation, hematologic observations, internal deposition of radionuclides, and general radiation injury from atomic weapons.

The exposed subjects were groups of Marshallese on three atolls, totalling 239 persons and 28 American service men on Rongerik atoll. Estimated total gamma doses in air ranged from 175 r to 14 r before evacuation was completed from the various islands to Kwajalein. Early clinical manifestations of gastrointestional symptoms and later granulocytopenia and thrombocytopenia were observed in the more heavily irradiated persons. Extensive skin lesions and epilation were largely confined to the more heavily exposed Marshallese on Rongelap and their pattern depended on the particulate form of the fallout material and the efficacy of decontamination. Color illustrations of skin lesions and microscopic preparations are included. More elaborate laboratory examinations were apparently limited by the facilities available. Least important clinically was internal deposition of fission products, notably Sr^{89}, Ba^{140}, rare earths, and I^{131}. Excretions and body burdens of radionuclides were studied to some extent. Some observations were made on the effects of calcium EDTA therapy.

This report should be of interest to all who may be concerned with policy decisions or medical management of situations involving fallout from thermonuclear weapons.

RICHARD H. CHAMBERLAIN, M.D.

RADIUM THERAPY; ITS PHYSICAL ASPECTS AND EXTENSIONS WITH RADIOACTIVE ISOTOPES. By C. W. Wilson, M.Sc., Ph.D., F.Inst.P., Principal Physicist to the Westminster Hospital, London. Second edition. Cloth. Price, $7.50. Pp. 286, with 73 illustrations and 51 tables. The Williams & Wilkins Co., Mt. Royal and Guilford Avenues, Baltimore 2, Maryland, 1956.

The first edition of this book was published in 1945, and filled a very real need. In the present revision the valuable parts of the original have been preserved or brought up to date, and a considerable amount of new information has been added. These additions mainly deal with radioactive isotopes, but some new material is interspersed throughout.

The chapters on interaction of high energy radiations with matter, and on gamma ray dosimetry, cover the subjects in a concise and straightforward manner. The radioisotope section is relatively brief, and mostly devoted to the physical properties of a few potential gamma ray emitters. It is explicitly stated in the preface that isotopes administered internally are not to be considered.

About half the book is devoted to dosage calculations, with many examples and excellent illustrations. As would be expected, the calculations are based on the Paterson and Parker charts and tables. No correlation is given between this dosage system and any other. It might have been worth while to have included the linear source table widely used in the United States, since this supplies information not available in the Paterson and Parker system. The importance of roentgenographic control of interstitial implants is stressed and several

methods mentioned, but none is described in working detail. Considerations of integral dose or total energy absorption have been introduced into every dosage section. The teleradium chapter has been extended to include the new powerful radioactive cobalt installations.

The matter of protection is well covered. Some data on measured exposures to radium workers make it evident that in the light of recent ICRP recommendations better procedures will have to be developed.

The format of the book is pleasing; the text is clear and free from typographical errors, and the illustrations are well reproduced. A list of references is appended to each of the ten chapters. Teachers and students of radium therapy, and all practicing radiotherapists should find this a valuable addition to their libraries.

Edith H. Quimby

Norme per le Protezioni contro le Radiasioni Ionizzanti. By F. Fossati, P. Gallone, L. Parmeggiani, C. Polvani, and M. Scolari. Cloth. Pp. 259, with 22 drawings and 39 tables. Ulrico Hoepli, Milan, Italy, 1956.

This volume, published by the Committee for Radiological Protection of the Italian Society of Medical Radiology, is a compilation and adaptation to local conditions of (1) the Recommendations of the ICRP (International Commission on Radiological Protection), revised in 1954, and published in 1955; (2) the DIN (German Industry Rules) 6811, 6812, and 6813, printed in 1954; and (3) the Handbooks of our National Bureau of Standards, up to No. 55, issued in 1954. These "norms" are suggestions, not regulations, and the authors warn that detailed legislative enactment in this changing field could interfere both with scientific progress and with everyday activity.

The introductory pages include various prefatory remarks, and a listing of bibliographic and other sources, detailed for each table and figure in the text. After a glossary of terms used in the manual and other general information, follows a special chapter devoted to maximum admissible dosages. Separate sections give the rules for protection against roentgen rays of 250 kv. or less; against roentgen rays of more than 250 kv.; against radiations emitted by telecurietherapy installations and particle accelerators; against natural and artificial radioactive substances used for external irradiation; and against internally administered radioisotopes. There are seven appendices: rules for the protection against radiation in industrial and scientific laboratories; rules for the transportation of radioactive material; rules for the disposal of radioactive wastes; rules for the protection against electrical hazards; rules for television receivers used by the general population; rules for the dosimetry of roentgen rays, gamma rays, electrons, and neutrons; and, finally, excerpts from all the regulations pertaining to radiologic protection, enacted in Italy by law or decree.

A detailed analysis of the rules is beyond the scope of a review, but a few quotations and remarks may be in order. As mentioned in the preface, references to ionizing hazards caused by atomic warfare are not discussed. Throughout the text, the term "admissible" replaces the word "permissible" to indicate the maximum dosage: it is certainly significant from a semantic viewpoint. The maximum admissible dosage from simultaneous external and internal exposure should not exceed 300 mrem weekly to any critical organ. The useful beam for roentgen diagnosis must be filtered up to 60 kv. with the equivalent of 0.5 mm. Al, up to 75 kv. with 1.0 mm. Al, beyond 75 kv. with 3.0 mm. Al; between 100 and 125 kv., 4 mm. Al or 0.2 mm. Cu are preferable, beyond 125 kv. 5 mm. Al or 0.3 mm. Cu. For roentgenoscopy, the target-table distance must be at least 35 cm. ($14\frac{1}{4}$ inches), while for roentgenoscopy with portable equipment, the target-skin distance should be at least 35 cm., and 3.0 mm. Al-equivalent must filter the useful beam. The ingenious formulas and realistic requirements of NBS Handbook 60 were apparently not available before completion of the manuscript. There is also no mention of special protective circumstances needed with image intensifiers and roentgen cinematography. Every protective device must be indelibly marked with its lead-equivalent value, determined at 80 kv. Total admissible body radiation in professionals should not exceed 0.6 rem weekly to the basal layer of the epidermis, or 0.3 rem weekly to the gonads, the hematopoietic system, or the lens; the equivalent dose in erg/g. (weekly) is 30 for roentgen and gamma rays, electrons and beta rays; it is 3 for neutrons and protons up to 10 mev., and for alpha particles from natural radioactivity; it is only 1.5 for heavy nuclei. The use of roentgenoscopy for the fitting of shoes is discouraged, but brief rules are offered for protection of the customer, and the maxi-

mum time limit of exposure is fixed at ten seconds. No mention is made of the autopsy following shortly after intake of radioactive material. Dosimetry of slow neutrons is accomplished with proportional counters using boron; for faster neutrons the counter is covered with paraffin, while for very fast neutrons (up to 20 mev.) the gas used is carbon dioxide.

The authors are to be commended for their painstaking care, the generally adequate provisions, and the reasonable suggestions offered. The volume belongs in any library devoted to radiologic physics, and it is easy to predict that these "Italian rules" for the protection against ionizing radiations will be extensively and repeatedly quoted in the universal literature.

E. R. N. Grigg, M.D.

Progress in Nuclear Energy. Series vii. Medical Sciences. Volume I. Edited by J. C. Bugher, The Rockefeller Foundation, New York; J. Coursaget, C. E. A. Saclay; and J. F. Loutit, Medical Research Council, A.E.R.E., Harwell. Cloth. Price, $6.00. Pp. 165. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 36, New York, 1956.

This volume of 160 pages is essentially a summary of that part of the material presented at the International Conference for Peaceful Uses of Atomic Energy held at Geneva in August, 1955 concerned with the Medical Sciences. It consists of forewords by R. S. Stone and E. R. Carling and of seven chapters covering various aspects of the subject.

Belcher and Mayneord, in their chapter entitled "Radioactive Isotopes in Medical Diagnosis," extend the review of this subject beyond the confines of the Conference and add an extensive and very up-to-date bibliography. Methods of physical measurement, radiography with radioelements, isotope dilution techniques, measurement of erythrocyte life span, blood circulation studies, detection and localization of tumors, and finally, metabolic and functional studies with the various isotopes of I, Fe, Co, Zn, etc., come in staccato sequence under brief, but critical review, thus easing immeasurably the task of the reader interested in assessing quickly the significant trends prevailing in this field.

In the article following, entitled "The Diagnosis and Investigation of Disease with Radioactive Isotopes," J. F. Ross skillfully confines himself to pertinent papers of the Conference and supplements the previous chapter by keeping the emphasis on the physiologic significance of the work reviewed.

In chapter three, Kozlova summarizes the clinical results obtained with Co^{60} therapy in the U.S.S.R. Special attention is called to the use of carotid ligation and vagosympathetic blockade in conjunction with radiotherapeutic treatment for the purpose of reducing local tissue reaction to radiation, and to the clinical impression that the latter is reduced by the use of Co^{60} instead of radium. J. S. Mitchell reports on the clinical use of Ir^{192} in about 300 cancer cases treated between 1950 and 1955, on a Ce^{144} beta-ray applicator and on his experience with a 30 mev. synchrotron; a valuable discussion as to the clinical indication for the use of the latter is included. M. Brucer discusses at some length his investigation on the possibilities and limitations of Cs^{137}, Co^{60}, $Eu^{152,154,155}$ as teletherapy sources. L. E. Farr concludes the chapter with a discussion of fundamental principles of neutron capture therapy and a description of the work thus far accomplished.

The fourth chapter deals with the use of radioactive materials in internal therapy and consists of a series of sections written by an outstanding collection of authors of international repute. Thus J. H. Lawrence discusses his extensive experience on the use of P^{32} in hematologic therapy and A. V. Kozlova, covering the same field, adds some observations and comments on the use of supplemental external radiation by conventional means. J. S. Mitchell discusses the use of I^{131} in hyperthyroidism and thyroid cancer and mentions some experimental studies taking shape at Cambridge. J. H. Muller reviews in some details his experiences with radiocolloids in the treatment of generalized carcinomatosis in the pleural and peritoneal cavities, and A. Chevallier and C. Burg discuss the use of chromic radiophosphate in interstitial therapy. This chapter ends with a notable contribution by V. H. Franco and colleagues on the accurate determination of thyroid mass by "pneumo-thyroid" roentgenographic techniques, and on the correlation between dose and therapeutic results obtained in the treatment of hyperthyroidism with I^{131}.

Chapter five consists, in essence, of a succession of heroic efforts to acquaint the reader with the philosophy underlying principles and standards of radiation safety: W. Binks, K. Suzue, L. S. Taylor, A. A. Letavet, P. Dorolle

and K. L. Goodall take turns in dealing with the various aspects of this complex problem which, if unrealistically appraised, may soon lead to bureaucratic efforts much more thorough and extensive than the scientific efforts essential for its elucidation. The bare facts on the matter are succinctly presented in the following chapter by A. J. Cipriani.

Last, but not least, is chapter seven on "Dosimetry of Ionizing Radiation," by G. Failla, who departs somewhat from the role of reporter to the Conference in order to review critically the subject of radiation dosimetry on the basis of the rad, and to summarize some of the notable contributions from his laboratory.

Your reviewer has found this volume of definite help in his efforts to appraise the medical implications of atomic energy as reported at Geneva, and the authors should be congratulated for a job well done.

L. D. MARINELLI

BOOKS RECEIVED

THE BIOLOGIC BASIS OF CANCER MANAGEMENT. By Freddy Homburger, M.D., Research Professor of Medicine, Tufts University School of Medicine; Scientific Associate, Roscoe B. Jackson Memorial Library. Cloth. Price, $10.00. Pp. 354, with 10 figures and 39 tables. Paul B. Hoeber, Inc., 49 East 33rd Street, New York 16, New York, 1957.

CHEMICAL ANTHROPOLOGY. By Icie G. Macy and Harriet J. Kelly. Price $3.75. The University of Chicago Press, 5750 Ellis Avenue, Chicago 37, Illinois, 1957.

LITHIASE DE LA VOIE BILIAIRE PRINCIPALE. By Pablo-L. Mirizzi, Professeur à l'Université de Cordoba (Argentine). Paper. Price, 2,200 fr. Pp. 162, with 79 illustrations. Masson et C^ie^, Éditeurs, 120 boulevard Saint-Germain, Paris 6^e^, France, 1957.

CLINICAL GASTROENTEROLOGY. By Eddy D. Palmer, M.D., F.A.C.P., Lieutenant Colonel, Medical Corps., United States Army; Consultant in Gastroenterology to The Surgeon General. Cloth. Price, $18.50. Pp. 630, with 216 illustrations. Paul B. Hoeber, Inc., 49 East 33rd Street, New York 16, New York, 1957.

THE PRINCIPLES AND PRACTICE OF DIATHERMY. By Bryan O. Scott, M.R.C.S., L.R.C.P., D.Phys. Med., Consultant in Physical Medicine, The Radcliffe Infirmary and Cowley Road Hospital, Oxford, The Churchill Hospital, Headington, and the Oxford Regional Hospital Board, England. Cloth. Price, $5.00. Pp. 192, with 146 illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

EFFECT OF RADIATION ON HUMAN HEREDITY. Report of a study group convened by WHO together with papers presented by various members of the group. Cloth. Price, $4.00. Pp. 168, with tables and figures. Columbia University Press, 2960 Broadway, New York 27, New York, 1957.

SAVOIR INTERPRÉTER; LA RADIOLOGIE PLEURO-PULMONAIRE. By Dr. L. Babaiantz, Professeur à la Faculté de Médecine de Lausanne; and Dr. F. Cardis, Chargé de cours à la Faculté de Médecine de Lausanne. Paper. Price, 5 Fr. Pp. 96, with 49 illustrations. Les Editions de Visscher, Bruxelles, Belgium, 1957.

BONE TUMORS. By David C. Dahlin, M.D., Consultant, Section of Surgical Pathology, Mayo Clinic; and Associate Professor of Pathology, Mayo Foundation, Rochester, Minnesota. Cloth. Price, $11.50. Pp. 224, with numerous illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

ADVANCES IN RADIOBIOLOGY. PROCEEDINGS OF THE FIFTH INTERNATIONAL CONFERENCE ON RADIOBIOLOGY HELD IN STOCKHOLM ON 15TH–19TH AUGUST, 1956. Edited by George Carl de Hevesy, Arne Gunnar Forssberg and John D. Abbatt. Cloth. Price, $15.50. Pp. 503, with numerous illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

PEDIATRIC ROENTGENOLOGY. By Dr. M. A. Lassrich, Prof. Dr. R. Prévôt, and Prof. Dr. K. H. Schäfer, Hamburg. Translation from the German provided by James T. Case, M.D., D.M.R.E. (Cambridge), Professor Emeritus, Radiology, Northwestern University Medical School, Chicago; Director, Memorial Cancer Foundation, Santa Barbara, California. Cloth. Price, $28.00. Pp. 328, with 700 illustrations. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, New York, 1957.

ROENTGEN DIAGNOSIS OF ABDOMINAL TUMORS IN CHILDHOOD. By Charles M. Nice, Jr., M.D., Ph.D., Alexander R. Margulis, M.D., and Leo G. Rigler, M.D., all from the Department of Radiology, University of Minnesota Medical School, Minneapolis, Minnesota. Cloth. Price, $4.00. Pp. 75, with 52 illustrations. Charles C Thomas, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

ELEVENTH ANNUAL REPORT OF THE OAK RIDGE INSTITUTE OF NUCLEAR STUDIES. Operating Under Contract with the United States Atomic Energy Commission. June 30, 1957. Paper. Pp. 86, with numerous illustrations. Oak Ridge Institute of Nuclear Studies. P. O. Box 117, Oak Ridge, Tennessee, 1957.

LUES CONNATA. By Dozent Dr. Med. Johannes Oehme, Oberarzt der Universitäts-Kinderklinik, Marburg an der Lahn, Früher Leipzig. Second edition. Cloth. Price, DM 26.—. Pp. 116, with 51 illustrations and 34 tables. Georg Thieme, Hainstrasse 17/19 Aufgang C, Leipzig C 1, Germany, 1957.

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ABSTRACTS OF RADIOLOGICAL LITERATURE

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INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

Nervous System

Nanson, E. M.: Thoracic meningocele associated with neurofibromatosis 180

Skeletal System

Greenwald, C. M., Meaney, T. F., and Hughes, C. R.: Chordoma—uncommon destructive lesion of cerebrospinal axis..... 180

Blood and Lymph System

Bonte, G., Caron, J., Pauchant, M., and Spy, E.: Examination of the mediastinal aorta with contrast agents (thoracic aortography). 180

Abrams, H. L.: Radiologic aspects of operable heart disease. III. The hazards of retrograde thoracic aortography: A survey..... 181

McAfee, J. G.: A survey of complications of abdominal aortography..... 181

Morino, F., and Tarquini, A.: Selective abdominal arteriography via the brachial artery..... 181

Fusi, G.: Considerations on the value of aortography in the vascular pathology of the abdominal aorta and the iliacs..... 182

RADIATION THERAPY

Cade, S., and Lee, E. S.: Cancer of the tongue; a study based on 653 patients..... 182

Friedman, M., and Pearlman, A. W.: Irradiation of advanced cancer of the head and neck through a grid. Part I. Study of absorbed dose by observation of skin and mucosal reactions..... 182

Watson, T. A.: Co^{60} telecurietherapy—after five years..... 183

Bennet, J. E.: Interim results of cobalt 60 therapy..... 184

Thomson, D. H., and Smith, I. H.: A $cobalt^{60}$ study in oral carcinoma after five years.... 184

Zuppinger, A., Frank, L., Renfer, H., Schreiber, A., and Tütsche, C.: Early experiences with the 31 mev. betatron..... 185

McCombs, R. K.: Proton irradiation of the pituitary and its metabolic effects. Memorial Fund Lecture..... 186

RADIOISOTOPES

Cerviño, J. M., Manaro, J. M., Maggiolo, J., and de Delfino, E. Z.: Diagnostic and therapeutic applications of radioactive iodine in thyroid diseases..... 186

Sheline, G. E., Koulischer, N., and Pickering, D.: Thyroidal accumulation of radioiodine in children..... 187

Russell, K. P., Rose, H., and Starr, P.: The effects of radioactive iodine on maternal and fetal thyroid function during pregnancy.... 187

MISCELLANEOUS

Trout, E. D.: The use of electron beams in industrial processes..... 187

Muth, H., and Schraub, A.: A new case of fatal, occupational radium poisoning..... 187

Hicks, S. P., Brown, B. L., and D'Amato, C. J.: Regeneration and malformation in the nervous system, eye, and mesenchyme of the mammalian embryo after radiation injury... 188

Cottier, H.: The effect of prolonged administration of cortisone and antibiotics on irradiated pulmonary tissue in rats..... 188

ROENTGEN DIAGNOSIS

NERVOUS SYSTEM

NANSON, ERIC M. Thoracic meningocele associated with neurofibromatosis. *J. Thoracic Surg.*, May, 1957, *33*, 650–662. (From: The Department of Surgery, University of Saskatchewan, Saskatchewan, Canada.)

In the past twenty-five years sporadic cases of thoracic meningocele have been reported. The notable feature of the majority of the recorded cases is that the patients have been suffering from neurofibromatosis and that they have had kyphoscoliosis of the thoracic spine. The author adds another case of this syndrome, *i.e.*, generalized neurofibromatosis, kyphoscoliosis, and intrathoracic meningocele, to the literature and reviews the previously recorded 26 cases with some interesting results.

The usual explanation of a posterior sulcus tumor in von Recklinghausen's disease is a neurofibroma. Yet, the author believes this to be extremely rare. A meningocele is a much more common entity in such a situation. Most of the cases of thoracic meningocele with neurofibromatosis have had preoperative diagnosis of thoracic neurofibroma. A preoperative myelogram in patient having neurofibromatosis and a posterior sulcus chest tumor will almost always make the diagnosis of meningocele or exclude it and thus it will contribute to the most intelligent treatment. Because of the apparent high mortality in removing these intrathoracic meningoceles, some writers doubt the advisability of operating unless the symptoms are progressive. The author feels that modern surgery makes the excision relatively safe provided careful closure of the meningocele neck is carried out.

The pathology of the 26 previously recorded cases was not well defined by the previous investigators. The author's case suggests that these meningoceles may not arise in the usual manner but that they may develop from degeneration within a neurofibroma which subsequently communicates with the subarachnoid space. They may commence as a dumbbell type of tumor. The cyst of his case had a wall of 0.2 cm. in thickness except in its lower portion where it was 2.6 cm. thick. In the latter area it had the structure of a neurofibroma. A myelinated nerve was also found in one area of the cyst.—*Paul C. Olfelt, M.D.*

SKELETAL SYSTEM

GREENWALD, CHARLES M., MEANEY, THOMAS F., and HUGHES, C. ROBERT. Chordoma—uncommon destructive lesion of cerebrospinal axis. *J.A.M.A.*, April 6, 1957, *163*, 1240–1244. (Address: C. M. Greenwald, 2020 E. 93rd St., Cleveland 6, Ohio.)

Chordomas are variable in their roentgenographic appearance and should be considered in the differential diagnosis of destructive lesions occurring anywhere along the cerebrospinal axis. They show a predilection for the extremes of the spinal axis, *i.e.*, the basioccipital and sacrococcygeal regions. Growth is slow with bone destruction from expansion. An extraosseous soft tissue component is a constant finding. The lesion is radioresistant. Signs and symptoms include nerve deficits corresponding to the level of the lesion.

Vertebral chordomas tend to exhibit polarity and may show local erosion of bony structures indistinguishable from primary intraspinal tumor. In the cervical region, nasopharyngeal air column indentation from soft tissue components with osteolytic vertebral body destruction and collapse may be observed. A lesion in the thoracic spine showing lytic bone destruction with paravertebral mass appearing similar to tuberculosis is illustrated. Cranial and sacrococcygeal chordomas, generally midline in location, tend to present less variation in roentgenographic appearance, the latter comprising 40–50 per cent of the cases studied. Preoperative diagnosis is possible in nearly half. Roentgen findings of a lobulated, midline, osteolytic defect with well defined margins and prolonged clinical course are suggestive but not pathognomonic. The extraosseous components may simulate pelvic mass of other origin especially if anteriorly located.

Cranial chordomas arise almost entirely from the region of the spheno-occipital synchondrosis and with anterior growth involve the sella turcica and parasellar structures. Sinuses and orbit may be involved and appear roentgenographically similar to neoplasm.—*Eldon D. Van Sandt, M.D.*

BLOOD AND LYMPH SYSTEM

BONTE, G., CARON, J., PAUCHANT, M., and SPY, E. Examen de l'aorte médiastinale par les agents de contraste. (Aortographie thoracique.) (Examination of the mediastinal aorta with contrast agents [thoracic aortography].) *J. de radiol., d'électrol. et de méd. nucléaire*, May–June, 1957, *38*, 459–466. (From: Service de Radiologie, Hôpital de la Charité, Lille, France.)

Opacification of the thoracic aorta is indicated to study coarctation, differentiation of aneurysms and tumors and to determine vascular involvement by tumors. The various methods of opacification are reviewed.

The authors prefer to use the Seldinger catheter, inserting it in a femoral artery and placing the tip in the region of the aortic arch. Forty cc. of 75 per cent vasurix (methylglucamine salt of acetylaminotriiodo-benzoic acid) is injected to study the aorta, and 15 cc. of the 50 per cent solution is used for selective angiography of the aortic branches.

Very few difficulties have been encountered with the method. One patient suffered a period of bradycardia for five minutes when the left coronary artery

was opacified. The catheter is inserted in the arm for study of coarctation.—*Charles M. Nice, Jr., M.D., Ph.D.*

Abrams, Herbert L. Radiologic aspects of operable heart disease. III. The hazards of retrograde thoracic aortography: A survey. *Radiology*, June, 1957, *68*, 812–824. (Address: Stanford University Hospitals, San Francisco, Calif.)

The author reports on the results of a survey on the hazards of retrograde thoracic aortography. Answers to the questionnaires sent to institutions in the United States, Canada, England, France, Sweden, Denmark, Germany and South America revealed that 29 deaths occurred in a total series of 1,706 thoracic aortographies. This represents a mortality of 1.7 per cent and includes all types and concentrations of media and sites of injection.

Most of the deaths and severe reactions appeared to be associated with cerebral damage although severe renal reactions were also noted as were cardiac and respiratory disturbances. The procedure of thoracic aortography should not be considered a simple roentgenologic study and there should be close collaboration between the physicians of the various specialties concerned in this field of study. The radiologist is the one upon whom the final responsibility should rest as to whether the information to be gained justifies the risk of the examination.

As a result of all the information submitted, the author lists and discusses a number of recommendations which should forestall severe reactions and diminish the risk of this procedure.—*Donald N. Dysart, M.D.*

McAfee, John G. A survey of complications of abdominal aortography. *Radiology*, June, 1957, *68*, 825–838. (Address: Department of Radiology, The Johns Hopkins Hospital, Baltimore, Md.)

To obtain information regarding the complications of abdominal aortography, a questionnaire was sent to 450 hospital radiologists and urologists. A total of 13,207 abdominal aortographies were collected from the replies to the questionnaire. In this collected series there were 37 fatalities attributable to the procedure, a mortality rate of 0.28 per cent. In addition, 98 serious nonfatal complications occurred (0.74 per cent).

There were 12 fatalities due to renal complications and 27 serious nonfatal renal damage. The risk of injury to the kidneys depends on the quantity of contrast medium reaching them. In one-third of the 39 serious injuries, the injection was made either directly into a renal artery or into the aorta at the origin of a renal artery. The influence of previously disturbed renal function on the incidence of renal damage could not be evaluated.

The incidence of all complications, including renal lesions, was lower with 75 per cent neo-iopax than with other contrast media. The incidence of all complications (including renal disease) was more than twice as great with 70 per cent diodrast than with 70 per cent urokon.

Neurologic damage was an important hazard with 5 fatal and 24 nonfatal complications. The danger appeared to be increased by the use of spinal or general anesthesia, by excessive injections of medium, and by the proximity of the needle tip to the major anterior radicular artery, usually at the level of L-2.

Less frequent complications include hemorrhage from the puncture site and cardiovascular, gastrointestinal, and general anesthetic disturbances. Detailed suggestions for reducing the incidence of these complications include the following: (1) a test roentgenogram after injection of 5 cc. of medium; (2) insertion of the needle at a high level; (3) use of local anesthesia; (4) avoidance of abdominal compression; (5) avoidance of excessive amounts of contrast medium (over 30 cc.); (6) use of only 10 to 15 cc. of medium in high aortic obstruction; (7) avoidance of direct puncture of an aortic aneurysm.—*Arno W. Sommer, M.D.*

Morino, F., and Tarquini, A. Arteriografia addominale selettiva per via omerale. (Selective abdominal arteriography via the brachial artery.) *Radiol. med.*, June, 1957, *43*, 529–550. (From: Istituto di Patologia Speciale Chirurgica dell'Università, Genova, and Centro di Cardiochirurgia "A. Blalock," annesso alla Clinica Chirurgica dell'Università, Torino, Italy.)

The technique adopted by the authors is essentially the one described by Bierman *et al.* (in this Journal, 1951, *66*, 555–568.)

After the exposure of the brachial artery at the level of the middle third of the arm, a No. 8 catheter is guided by roentgenoscopy to the aortic arch and through the aortic hiatus into the abdominal aorta. When the tip of the catheter is at a level with the branch which is to be visualized, a few cc. of 1 per cent novocaine is injected in order to prevent a vascular spasm. After one minute or two, 4 to 8 cc. of contrast medium is rapidly introduced and at the same time seriograms are taken.

The authors feel that this method of selective visualization of the branches of the abdominal aorta is not a difficult procedure and is by far safer than translumbar aortography. The contrast medium, in their opinion, that gives less reaction is 50 per cent hypaque.

This procedure has been carried out in 34 patients, with a total of 51 arteriographies, for visualization of the celiac artery (10 cases), the splenic artery (11 cases), the hepatic artery (8 cases), the renal artery

(20 cases), and the superior mesenteric artery (2 cases).

Seventeen cases are reported and the various vascular patterns are analyzed and discussed.—*A. Govoni, M.D.*

FUSI, GIORGIO. Considerazioni sul valore dell'aortografia nella patologia vascolare dell'aorta addominale e delle iliache. (Considerations on the value of aortography in the vascular pathology of the abdominal aorta and the iliacs.) *Nuntius radiol.*, March, 1957, *23*, 228–257. (From: Istituto di Radiologia dell'Università di Roma, Rome, Italy.)

The author, on the basis of his experience and that of others, analyzes and discusses the different techniques, indications, contraindications, and complications of abdominal aortography.

The clinical findings and vascular patterns of the various types of endarteritis, arterial occlusions and aneurysms are reviewed and discussed. The importance and value of abdominal aortography in vascular surgery is pointed out.

The illustrations are excellent and the bibliography up-to-date, especially regarding the European literature.—*A. Govoni, M.D.*

RADIATION THERAPY

CADE, STANFORD, and LEE, E. STANLEY. Cancer of the tongue; a study based on 653 patients. *Brit. J. Surg.*, March, 1957, *44*, 433–446. (From: Westminster Hospital, London, England.)

The senior author and his colleagues have seen 653 cases of carcinoma of the tongue since 1925, most of them at the Westminster Hospital.

The usual age distribution is reported (peak at sixty-eight years). The sex ratio has fallen from 10 males to 1 female in 1925 to 2 males to 1 female in recent years. A general decrease of deaths from carcinoma of the tongue in Great Britain is due entirely to decrease of the disease in males (probably due to the decrease of that type of carcinoma associated with syphilis, severe oral sepsis and leukoplakia).

Multiple primary lesions occurred in 4.1 per cent. All but 8 lesions were squamous cell carcinoma. In discussing diagnosis the authors state that the most common cause of ulcer of the tongue in Great Britain is carcinoma.

Most of the lesions were in the anterior two thirds of the tongue and were treated with radium implants, usually single plane application. The optimal dose rate seemed to be 30 to 60 r per hour to a total of 7,000 r (or more in smaller lesions). A total of 573 implants were performed in 507 cases with an operative mortality of 2.6 per cent. The authors avoid large volume implants and deprecate combinations of interstitial and external radiation therapy.

Teletherapy using gamma or 2 million volt sources was the treatment of choice for posterior tongue lesions (85 per cent had enlargement of the deep cervical lymph nodes) and for palliation. Tumor doses of 7,000 r in five to six weeks were attempted.

Radical surgery for the primary lesion was considered to be too mutilating and was usually limited to recurrences and radioresistant lesions.

Enlarged cervical lymph nodes were present in 57.5 per cent of all patients when first seen. Full block resection was performed whenever possible (117 cases, 17 per cent) after the primary lesion was controlled. Neither partial (submandibular) nor prophylactic neck dissections were undertaken. Teletherapy or radium implantation in the neck was used whenever surgery was not possible.

Over-all five years survival was 27 per cent in the determinate cases (24 per cent for all cases). Five year survival for those with involvement of the anterior two thirds of the tongue was 35 per cent whereas only 11 per cent of those with posterior third involvement survived. If enlarged lymph nodes were present when the patient was first seen, 14 per cent lived five years, whereas 51 per cent of those without enlarged lymph nodes initially lived five years.

Other unfavorable factors were a large primary lesion (over 2 cm. in size) and the primary lesion crossing the midline or involving adjacent structures. Survival figures for females were better than for males due entirely to the earlier lesions in the women. Degree of cellular differentiation did not seem to have any prognostic value.—*Henry J. Klos, M.D.*

FRIEDMAN, MILTON, and PEARLMAN, ALEXANDER W. Irradiation of advanced cancer of the head and neck through a grid. Part I. Study of absorbed dose by observation of skin and mucosal reactions. *Radiology*, June, 1957, *68*, 852–859. (Address: M. Friedman, 1016 Fifth Avenue, New York 28, N. Y.)

A comparative study of the "grid" and "open-portal" techniques was made by irradiating, through one field, two groups of patients having squamous-cell carcinoma of the head and neck. The size of the portals and over-all treatment times were similar. The grid had perforations of 1 square cm., with 45 per cent of the area open. The quality of radiation was of a half-value layer of 1.0 to 1.5 mm. Cu.

The doses for each technique were grouped in a higher and lower dose range. Similar severe maximum skin reactions were produced by 7,100 to 8,000 r (measured with backscatter) with the open-portal technique and 15,100 to 20,000 r (air) with the grid technique. The average epidermitis with the two techniques was of second degree intensity, healed in seven to nine weeks, and was approximately equivalent. The lower grade of skin reaction was produced by dose levels of 6,100 ro 7,000 r (measured with backscatter) for the open-portal and 10,100 to 15,000 r (air) for the grid technique.

With doses producing similar skin reactions, the grid technique delivered larger effective doses in the depth. The findings suggest that measured doses through a grid are approaching reasonable accuracy.—*Arno W. Sommer, M.D.*

Watson, T. A. Co^{60} telecurietherapy—after five years. *J. Fac. Radiologists*, June, 1957, *8*, 22–26. (From: Saskatoon Cancer Clinic, City Hospital, Saskatoon, Saskatchewan, Canada.)

The structure of the Saskatoon unit has been exhaustively described elsewhere. The output at the beginning was approximately 40 r/min. at 80 cm., equilibrium with scattering material being established.

The most important consideration is the selection of patients for supervoltage therapy. This method of treatment does not take the place of medium voltage or superficial roentgen therapy, nor of local radium or radon applications.

Supervoltage radiation, compared with that of 200–400 kv. provides a higher depth dose (especially where small fields are used), a lower integral dose for the same volume irradiated, much less skin reaction for the same given dose, and less differential absorption between bone and cartilage and other tissues. Furthermore, while large fields can be obtained at reasonable focal skin distances with roentgen-ray apparatus, the same is not true of cobalt 60 beam therapy machines. Sometimes, for lesions near the surface, the lower percentage depth dose of medium voltage roentgen rays may be preferable, if a short distance supervoltage unit is not available.

Possibly, a qualitative difference in biologic effect exists between the two energy ranges. This is based on the fact that the mean linear ion density produced by high energy photons is very much less than that of medium energy photons.

"*Head and Neck*" (145 cases) includes tumors of the mouth, lip, tongue, pharynx, larynx, thyroid, salivary glands and brain. Almost all of these tumors have been treated by either cobalt 60 telecurietherapy, medium voltage roentgen rays or locally applied radium or radon. Cancers of the tongue, floor of mouth and lip are best treated by radium (or radon) implantation or mould application since here it is easy technically to apply a high dose to a limited volume, with a rapid fall-off of dose in surrounding normal structures, and at the same time use high energy radiation with its lesser absorption in bone and cartilage. Larger lesions in this region are better treated by supervoltage therapy because, compared with medium voltage, there is less chance of bone or cartilage necrosis and skin reactions are much less severe. Cobalt 60 beam therapy is also preferred over 200 kv. therapy for the same reasons in cancers of the larynx and pharynx. Medium voltage therapy is usually preferred in tumors of the salivary and thyroid glands for a high depth dose is actually undesirable in that unnecessarily severe mucosal reactions over wide areas may be produced. Tumors of the brain are better treated by supervoltage radiation, due to the shielding effect of the skull. Epilation also tends to be less permanent and skin reactions less severe.

"*Deep*" *tumors—e.g.* (108 cases) cancer of the esophagus, inoperable cancer of the lung, or large cancers of the bladder—are obvious choices for supervoltage therapy. The large depth dose, the relative absence of skin reactions, the lesser incidence of radiation sickness and the lesser absorption in bone are self-evident advantages. The same arguments apply when external radiation is used in cancers of the cervix or uterus.

"*Breast*" (327 cases). When primary radiation treatment is indicated, the author prefers to use medium voltage roentgen therapy, since a large area must be covered and, when a three or four field arrangement is used tangentially, a high percentage depth dose is not of great advantage. The cobalt 60 unit is used in the postoperative treatment of the axilla and supraclavicular regions, with parallel opposing fields front and back. In this way a higher dose can be obtained at the apex of the axilla, the danger of bone necrosis is minimized, and skin reactions are negligible. In general, distant metastases from carcinoma of the breast, when they occur in soft tissue near the surface are more suitably treated by medium voltage roentgen therapy. When metastases occur in bone, however, supervoltage radiation is indicated, since we are attempting to irradiate the soft tissue recurrence rather than the inorganic bone.

The heading "*Reticuloses*" (38 cases) includes all types of lymphosarcoma, reticulum cell sarcoma, Hodgkin's disease and leukemias. In all of these diseases very large fields are employed with medium voltage roentgen therapy. The use of medium voltage allows much greater flexibility as far as irregularly shaped fields and screening are concerned. Since the doses used with these large fields are not great, skin reactions are not a limiting factor.

The actual proportion of patients treated by supervoltage therapy (which, as well as those treated on the cobalt 60 unit, includes the few treated by 23 mev. roentgen rays) was 37 per cent.

Since no new therapeutic principle has been demonstrated with the advent of supervoltage radiation, it is doubtful that any significant improvement in five year survival results will occur. However, there is a marked gain from the point of view of technical ease in delivering a desired dose to any depth, and of comfort to the patient during and after treatment due to the absence of troublesome skin reactions, to the lesser liability to radiation sickness, and to the lesser danger of bone and cartilage necrosis. The latter points are of considerable importance in palliative therapy.

The author experienced no late unexpected com-

plications from supervoltage therapy—such as subcutaneous fibrosis or perforation of the stomach and small bowel which have been reported elsewhere. A few instances of necrosis of cartilage after treatment of cancer of the larynx, and one case of necrosis of the jaw, demonstrating that, in spite of the lesser differential absorption of bone and cartilage at high energies, the dangers of necrosis are not eliminated.

The dosage levels (in roentgens) are approximately 8 to 10 per cent higher than those formerly used with conventional roentgen therapy for comparable lesions.—*Stephen N. Tager, M.D.*

BENNET, JAMES E. Interim results of cobalt 60 therapy. *J. Fac. Radiologists*, June, 1957, *8*, 27–30. (From: Radiotherapy Department, Winnipeg General Hospital, Winnipeg, Manitoba, Canada.)

An Eldorado Cobalt Beam Unit Model A was installed by the Manitoba Cancer Institute in Winnipeg General Hospital in March, 1953. The source, 1,200 curies of cobalt 60, delivered approximately 32 r per minute to an average size field at 80 cm. source-skin distance. The source was renewed early in 1955, the strength this time being 1,800 curies, and the output approximately 48 r per minute to an average sized field at 80 cm. source-skin-distance. Of 1,200 cases treated, only a small proportion can be presented now due to many factors, notably previous treatment by other methods of irradiation, too small a number of specific disease to make a series.

Admittedly, carcinoma of the cervix (15 cases) is not treated solely by the cobalt 60 beam, but by a combination with intracavitary radium, using a modified Manchester technique. This group was given 50 mg. of radium in the cervical canal and 20 mg. of radium in each fornix, for a total of 33 hours in one application, the estimated dose at Point A being 4,000 r and Point B being 1,000 r. This was followed by cobalt 60 beam therapy to the whole pelvis, using 4 fields, 2 anterior and 2 posterior, angulated inwards at 45° and directed by means of the "pin and arc" method; 4,000 r was given to the whole pelvis in three weeks.

Carcinoma of Buccal Aspect of Cheek (11 cases). All of these cases were fairly advanced and the tumor was large although no actual lymph node involvement was present. In 1953 the tumor dose was 6,000 r, the maximum tissue dose being 6,500 r. The single field was applied at an angle. A back pointer was used to direct the beam to include the whole lesion but to exclude the opposite parotid in an endeavor to avoid a completely dry mouth. Those of the 1953 patients still surviving with no evidence of tumor have as a postradiational syndrome only two complaints. One is some partial dryness of mouth, easily relieved by chewing gum or eating food, the other a definite loss of mobility of the temporomandibular joint.

Carcinoma of the Rectum (37 cases). This group has obtained considerable palliation. Patients were referred after abdominoperineal excision had been carried out and disease had been found to be still present in the pelvis. In most cases actual fungating tumor was growing through the perineal scar. All patients had relief of pain for varying periods. In nearly all, the tumor although relatively radioresistant, regressed markedly. In all patients the tumor was described pathologically as an adenocarcinoma, Grade 2.

Carcinoma of the Larynx (17 cases). The number of palliatively treated cases is twice the number of radically treated cases. In the palliative cases, with only one exception, all of the patients had metastatic tumor in one or both cervical lymph node regions. The palliative cases are not classified as either extrinsic or intrinsic laryngeal lesions. The radically treated laryngeal tumors responded much as might have been expected. With one exception, a patient who died five months after treatment, all are alive with no evidence of tumor, the survival time varying from thirteen months to twenty-three months.

Bronchogenic Carcinoma (36 cases). Those who have lived longest had a larger dose given but not all those given a large dose lived very long. Results are more or less comparable with results of more conventional types of therapy.

Carcinoma of the Bladder (56 cases). Most of these patients were referred because the tumor was inoperable. Very few early tumors were treated.—*Stephen N. Tager, M.D.*

THOMSON, D. H., and SMITH, IVAN H. A cobalt^{60} study in oral carcinoma after five years. *J. Fac. Radiologists*, June, 1957, *8*, 31–35. (From: The Ontario Cancer Foundation, London Clinic, London, Ontario, Canada.)

Oral carcinoma, unlike cancer of certain sites such as larynx and lung, requires more than a two or three year follow-up study period to be of any significant cure rate value.

The authors have not substituted cobalt 60 beam therapy in treating the early lesions satisfactorily amenable to radium needle or radon seed implantation. Analysis, therefore, is compiled mostly from those cases treated by radical cobalt 60 dosage, in size beyond the range of mould application or implantation.

The following tables record the number of oral cases treated by radical and palliative cobalt 60 beam therapy respectively (Table I), and indicate the distribution of lesions by site treated radically (Table II).

The impressions gained are, briefly:

(1) Roentgenographic evidence of invasion of the mandible by tumor growth is not necessarily a contraindication to cobalt 60 beam therapy. Four cases

TABLE I

ORAL CARCINOMA TREATED BY COBALT 60 BEAM THERAPY (1952–1955)

Radical Therapy	50
Palliation	29
Total	79

TABLE II

ORAL CARCINOMA BY SITE TREATED BY RADICAL DOSAGE COBALT 60 BEAM THERAPY (1952–1955)

Buccal Aspect	7
Palate and Upper Alveolus	5
Floor of Mouth and Lower Alveolus	17
Tonsil and Fauces	14
Tongue	7
Total	50

are included which revealed, on admission, definite roentgen evidence of mandibular invasion. All 4 patients experienced not only complete regression of tumor but early total repair of overlying mucosa. One patient, aged eight-six, died of intercurrent disease without evidence of cancer twenty-eight months following treatment. The remaining 3 are without pain, disease, or clinical recurrence of fistula eighteen, forty-five and fifty-four months following treatment. Two detailed examples are cited.

(2) Recurrence of disease subsequent to roentgen therapy has been successfully treated by cobalt 60 beam therapy. Five cases had been previously treated elsewhere with roentgen therapy. Of the 4 surviving cases, 3 are not only alive, but are without complication.

(3) Adjacent solitary lumph node invasion if included in the treatment field shows favorable initial regression. Nine of the 50 radically treated cases had clinically positive solitary lymph nodes sufficiently close to the primary disease to be included in the treated volume. None of these cases had surgery following therapy. All enlarged lymph nodes except one have either completely regressed or are regarded as clinically inert.

(4) The optimal tumor response lies in the 6,000 r to 7,500 r range delivered in four to six weeks.

(5) Skin reactions are less than from conventional roentgen therapy. How significant is it clinically? In 10 cases, a single field was used without intervening bolus, wax or plaster. The given dose ranged from 6,000 r in three weeks to 7,000 r in four and a half weeks, the tumor doses ranging from 5,000 r in three weeks to 6,300 r in four and a half weeks. In no case was there a moist desquamation.

With parallel opposing or tangential fields the situation is slightly different. Of 21 cases using this technique, 10 cases were treated without plaster, 9 cases using a plaster cast, and 2 cases utilizing a plaster cast and wax bolus. Reactions vary considerably within this group and are higher, of course, when fields are tangential, when skin lies within the tumor volume, and when plaster with or without wax is used.

(6) Mucosal reactions are decidedly more variable. Mucosal reactions fall into three categories. It is most common, using the standard tumor dosage of 1,500 r per week, for the reaction to come up during the third week, quickly reach a maximum and continue unchanged through to the end. Less commonly, a more slowly appearing reaction occurs, gradually reaching fibrinous proportions during the fourth week. This allows scope in resistant types of lesions to push on to 7,000 r before a heavy fibrinous reaction will appear.

Mucosal reaction, while heavy as a rule, is of much shorter duration than that of conventional roentgen therapy.

(7) As with other ionizing rays, certain oral carcinomas exhibit extreme resistance. The criteria were persistence of tumor, or recurrence of the primary disease within three months of completion of treatment. Only 3 cases, of 50 radically treated, could be categorized as being resistant.

One senses an added safety to bone when using cobalt 60 beam therapy. It should be thus, with the lessened coefficient of absorption. In 43 cases radically showing no clinical or roentgenographic evidence of tumor invasion of the mandible at the commencement of treatment, no spontaneous bone necrosis has occurred.

(8) The clinical response thus far augurs well. Carcinoma of fauces and tonsil and carcinoma of floor of mouth and lower alveolus were selected for detail, primarily because they comprise the largest numbers in the series.

Of the entire oral group treated radically prior to 1955, 22 of 23 patients are without disease twenty-four to twenty-five months. Of 50 patients treated similarly through 1955 there are 33 alive and free of disease twelve to twenty-four months. Next to larynx, cobalt 60 beam therapy will find its greatest curative effectiveness in oral carcinoma.—*Stephen N. Tager, M.D.*

ZUPPINGER, ADOLF; FRANK, LISELOTTE; RENFER, HANSRUDOLF; SCHREIBER, ADAM; and TÜTSCHE, CONRAD. Früherfahrungen mit dem 31-MeV-Betatron. (Early experiences with the 31 mev. betatron.) *Strahlentherapie*, March, 1957, *102*, 407–418. (From: Röntgeninstitut der Universität und des Inselspitals, Bern, Switzerland.)

Physical measurements of the betatron beam were

made with the Victoreen r-meter. The betatron's 31 mev. beam is about 0.7 as effective as 250 kv. roentgen rays insofar as general therapeutic results with malignant tumors are concerned. The 31 mev. beam has a relatively more intensive effect on mitosis than conventional roentgen rays. Since these two observations are at variance, the authors suggest that the over-all therapeutic effect of these two types of ionizing radiation is not a function of effect on mitosis. Further, they suggest that the betatron's greater effect on mitosis makes it preferable in preoperative treatment of malignant tumors, particularly bronchial and gastric tumors.

Irradiation with the betatron produced good palliative results and a significant number of symptom-free patients in conditions unqualifiedly incurable by previous radiation methods.—*Henry G. Moehring, M.D.*

McCOMBS, ROLLIN K. Proton irradiation of the pituitary and its metabolic effects. Memorial Fund Lecture. *Radiology*, June, 1957, *68*, 797–811. (Address: Donner Laboratory, University of California, Berkeley 4, Calif.)

Preliminary studies were done to determine the effects of high speed particles on the rat hypophysis. Initial results were encouraging, and pituitary irradiation of monkeys, normal dogs, and dogs with breast cancer was undertaken. The biologic effectiveness of the high energy deuteron and proton beams was found to be close to that of 200 kv. roentgen rays.

When large single doses of more than 5,000 rad of deuterons or protons were given to the pituitary gland of animals, the final result was found to be the same regardless of the size of the dose. There was progressive atrophy of the entire gland accompanied by reduction in function. The higher the dose, the sooner the physiologic effects became apparent.

After these preliminary animal studies, the use of the proton beam for irradiation of the human pituitary gland was undertaken. Between September, 1954 and September, 1955, 26 patients with metastatic breast cancer received pituitary irradiation. Patients were selected for irradiation on the basis of several criteria: (1) There must have been objective evidence of progressing metastasis. (2) The patient should have received all indicated conventional surgical and radiation treatment. (3) The patient should have received a trial of hormone therapy, adrenalectomy, and removal or roentgen irradiation of the ovaries. Proton irradiation of the pituitary was carried out in fractionated doses, three times weekly. The first patient received 14,000 rad during a sixty-three day interval. Some of the later patients received as much as 30,000 rad in six treatments within a two week period. Sixteen patients had previously undergone bilateral adrenalectomy and oophorectomy. Nineteen of the patients had bone metastases.

Twenty-two of the 24 deceased patients have come to necropsy. Two patients still survive, both sixteen months postirradiation. Histologic evidence of damage was apparent in all patients who received over 20,000 rad, regardless of the interval between irradiation and death. No gross evidence of injury was detected in the brains or cranial nerves.

These studies have demonstrated that it is possible to destory a deep-seated organ without damage to intervening tissues. Pituitary function can be depressed and the pituitary can be destroyed without subjecting the patient to a craniotomy. This technique may be of value in the treatment of pituitary tumors, malignant exophthalmos and Cushing's disease.—*Arno W. Sommer, M.D.*

RADIOISOTOPES

CERVIÑO, J. M., MANARO, JULIO MORATÓ, MAGGIOLO, JORGE, and DE DELFINO, E. ZALDÚA. Aplicaciones diagnósticas y terapéuticas del yodo radioactivo en las afecciones tiroideas. (Diagnostic and therapeutic applications of radioactive iodine in thyroid diseases.) *Radiología*, Panamá, June, 1957, *7*, 95–110. (From: Instituto de Endocrinologia, Ministerio de Salud Publica, Montevideo, Uruguay.)

The authors report their experiences based on 80 tracer studies and 56 therapeutic studies with radioactive iodine since 1952. Uptake determinations over the thyroid and urinary excretion studies were done. Urinary excretion in forty-eight hours varied from 7–45 per cent in hyperthyroid patients, 44–88 per cent in euthyroid, and 48–83 per cent in hypothyroid patients.

Errors are induced by previous iodide medications in the preceding three months, antithyroid medication, thyroid preparations and low iodide diet.

Advantages of radioactive iodine in diagnosis are lack of influence by cooperation or emotional status of patient, ability to use the test when the basal metabolism test is affected by other diseases, and the fact that the test is more constantly accurate than the basal metabolic rate.

Disadvantages are that it cannot be used in regions where there is lack of iodine in diet and water, it is more expensive and requires special apparatus.

In 56 patients treated for hyperthyroidism, cure was obtained in 77.6 per cent by a single dose and in 18.3 per cent more by the second dose (total 96.9 per cent); diffuse goiters in young individuals are more sensitive than the nodular goiter.

Indications for radioactive iodine therapy include diffuse goiter in patients over forty-five who do not wish to have surgery, postoperative recurrence, hyperthyroidism in cardiac patients and sometimes in severe exophthalmos. Contraindications include young patients (fear of cancer), pregnancy and lactation.

Advantages and disadvantages of therapy are presented. Results in the authors' series are given in detail—*Charles M. Nice, Jr., M.D., Ph.D.*

Sheline, Glenn E., Koulischer, Nina, and Pickering, Donald. Thyroidal accumulation of radioiodine in children. *A.M.A. Arch. Int. Med.*, April, 1957, *98*, 391–395. (From: Departments of Radiology and Pediatrics, University of California School of Medicine, San Francisco, Calif.)

A significant contribution to the meager and controversial literature concerning the pediatric use of I^{131} in tracer studies of the thyroid gland is presented without comment as to the advisability of the procedure.

The full twenty-four hour uptake curves of 34 clinically euthyroid, 16 primary hypothyroid, 16 secondary hypothyroid and 17 hyperthyroid children are recorded and reveal no correlation between the age of the child and the thyroid uptake of I^{131}. The thyroid uptake was useful in distinguishing between hyperthyroidism, euthyroidism, and primary hypothyroidism but did not separate mild secondary hypothyroid children from the euthyroid group even after TSH stimulation.—*Joseph S. Bean, M.D.*

Russell, Keith P., Rose, Harvey, and Starr, Paul. The effects of radioactive iodine on maternal and fetal thyroid function during pregnancy. *Surg., Gynec. & Obst.*, 1957, *104*, 560–564. (From: Department of Obstetrics and Gynecology of The Moore-White Medical Clinic and the Department of Medicine of the University of Southern California School of Medicine, Los Angeles, Calif.)

The authors had the opportunity to observe two babies whose mothers had been treated with I^{131} for thyroid carcinoma early in pregnancy.

A thirty-three year old primigravida received 225 mc of I^{131} for recurrent carcinoma of the thyroid at about three months of pregnancy. In spite of maternal protein bound iodine (PBI) levels of from 2 to 3.8 micrograms, pregnancy proceeded to term and a normal appearing baby was delivered. At birth the cord blood showed a PBI level of 2.6 μgm. This rose to 5.8 μgm. after thyroid was administered beginning at two months of age.

The second patient had been on desiccated thyroid after resection of a papillary carcinoma. She became myxedematous upon discontinuing the drug in an attempt to abort a pregnancy without success. At about thirteen weeks of gestation she received 75 mc of I^{131} in divided doses for treatment of a metastasis. At term the cord blood PBI was 3.2 μgm. but dropped to 1.4 μgm. in nine days. Thyroxine was begun and the PBI rose to 6 μgm. The baby died of a respiratory infection at thirteen weeks and no thyroid could be found at autopsy.

The authors point out that the hazard of I^{131} to the fetus is the results of the high avidity of its thyroid for iodides. They believe that cord blood PBI determinations are valuable in the diagnosis of congenital hypothyroidism. (In 21 normal newborns the authors state that a mean PBI level of 7.7 μgm. was found in the cord blood whereas the maternal value was about 10 per cent higher.)—*Henry J. Klos, M.D.*

MISCELLANEOUS

Trout, E. Dale. The use of electron beams in industrial processes. *Radiology*, May, 1957, *68*, 708–713. (Address: 4855 Electric Avenue, Milwaukee 1, Wisc.)

The author discusses the use of high energy electron beams in industrial processing. The nonmedical use of electron beams is not new. Prior to the last few years, however, it was limited to scientific studies rather than to any large-scale practical application.

The field of food preservation is probably receiving more attention than any other. Numerous investigators are conducting food sterilization programs. Treated food has remained sterilized up to nine months but there has been a disturbing change in the taste of the treated foods. Vitamin loss is reported to be of the same order of magnitude as that encountered in heat processing. To accomplish food sterilization, the absorbed dose must be in the order of a few thousand to a few million rep. The modern 1 to 2 million volt therapy machines now in use are not adequate for most continuous production processes. Maximum electron penetration is about 0.5 cm. of unit density material per million electron volts. Hence a package of unit density material 3 inches thick would require a 15 mev. beam.

High energy electrons can produce a wide variety of chemical effects. Plastics subjected to irradiation have greater form stability and higher solvent resistance than the unirradiated material. Low dose irradiation produces a material so stable that it can be steam sterilized. Polyethylene tape subjected to irradiation is able to withstand high temperatures. Some plastic materials are depolymerized by irradiation. Dextran, which is used as a blood extender or substitute for plasma, is produced in this manner

The use of high energy electrons in industry has posed some new and difficult protection problems. Each new application of ionizing radiation to medical and industrial fields creates new problems as it makes its contribution to the total population radiation exposure.—*Dean Nichols, M.D.*

Muth, Hermann, and Schraub, Alfred. Über einen neuen Fall von gewerblicher Radiumvergiftung mit tödlichem Ausgang. (A new case of fatal, occupational radium

poisioning.) *Strahlentherapie*, April, 1957, *102*, 575–581. (From: Max Planck-Institut für Biophysik, Frankfurt a. M., Germany.)

This report concerns itself with the physical measurements pertaining to a patient fatally poisoned by radium. The clinical history of this patient has already been published by A. Gebauer and R. Heinecker in *Strahlentherapie*, 1955, *98*, 558. The patient was a chemist who died at the age of forty-eight years. He had worked with concentrated solutions of radium 226 and radium 228 and with thorium 228. For fifteen years, from 1933–1948, he had worked in a radium plant. This plant was bombed out in 1944 so that he transferred the work to his home. Then from 1948–1952 he did the same work on a private basis. His first symptoms appeared in 1948 consisting of dyspnea on exertion, dry cough, severe anterior chest pain, and a feeling that the chest was being constricted. At this time roentgenologic changes were demonstrable in the chest in the form of pulmonary fibrosis. The findings on chest films and his symptoms grew gradually worse until 1953 when an acute pulmonary inflammation caused his death. Throughout all this time, his peripheral blood picture remained normal.

From measurements made at and after postmortem examination, the body burden of radium 226 was established at 0.6×10^{-7} grams and of radiothorium at 0.3×10^{-7} curies. These levels are not extremely high and are within the range of maximum permissible levels. However, alpha-activity was measured well above the levels expected from the foregoing. This was demonstrated to yield a total value of about 4 microcuries and to come from polonium 210.—*Henry G. Moehring, M.D.*

Hicks, Samuel P., Brown, Barbara L., and D'Amato, Constance J. Regeneration and malformation in the nervous system, eye, and mesenchyme of the mammalian embryo after radiation injury. *Am. J. Path.*, May–June, 1957, *33*, 459–482. (From: Departments of Pathology, New England Deaconess Hospital and Harvard Medical School, Boston, Mass.)

Abnormal development following irradiation has been studied frequently in lower vertebrates, but less often in mammals. It is the purpose of this paper to demonstrate that radiation can extirpate specific cells or parts of the embryo and that regeneration and malformation in mammals is basically similar to that in other vertebrates.

Pregnant albino rats were irradiated (200 r at 250 kv.) on various days of gestation, then feti were removed at various intervals (from one to four samples in the same mother on different days). These feti were sectioned and compared with normals and with older offspring from the same litter.

A time table was then set up demonstrating at which phases of development the radiation was capable of causing sufficient damage to specific tissues which in turn resulted in specific abnormalities, such as anencephaly. At other phases of development the same amount of damage resulted in no malformations. Irradiation thus shows promise as a tool for experimental mammalian embryology.

Specific defects and their mechanisms are discussed. Photomicrographs are appended.—*Henry J. Klos, M.D.*

Cottier, Hans. Wirkungen einer langdauernden Gabe von Cortison und antibiotischen Mitteln auf röntgenbestrahltes Lungengewebe der Ratte. (The effect of prolonged administration of cortisone and antibiotics on irradiated pulmonary tissue in rats.) *Strahlentherapie*, May, 1957, *103*, 77–90. (From: Röntgeninstitut der Universität, Bern, Switzerland.)

One hundred and twenty rats were divided into groups of 10 and then subjected to various dosages of cortisone or antibiotics, or both, after or without irradiation. The rats irradiated received 3,000 r to a 2×1.5 cm. field of one lung.

High doses of cortisone (10 and 20 mg. of cortisone acetate per kilogram of body weight per day) yielded poor results. Mortality was increased. Pulmonary complications were more numerous even though the tendency of the irradiated lung to fibrose was decreased.

Lower doses (2 mg. of cortisone acetate per kilogram per day) showed no constant effect. Similarly, treatment with antibiotics (penicillin and streptomycin) produced no constant effect.

These animal experiments give no evidence in favor of prolonged administration of cortisone after pulmonary irradiation.—*Henry G. Moehring, M.D.*